

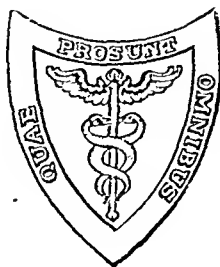
THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.
EDITOR

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NEW SERIES

VOL. CLXXXV



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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
JANUARY, 1933

ORIGINAL ARTICLES.

THE CONTROL AND COMPLETE REMISSION OF POLYCYTHEMIA
VERA FOLLOWING THE PROLONGED ADMINISTRATION
OF PHENYLHYDRAZIN HYDROCHLORID.*

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A CONCEPTION of the history and the present status of the treatment of polycythemia vera by means of phenylhydrazin hydrochlorid may be obtained by reviewing the papers of Eppinger and Kloss,⁷ Taschenberg,¹⁶ Levi,¹² Owen,¹⁴ Brown and Giffin,⁵ Bryan,⁶ Giffin and Conner,¹⁰ and by the experimental studies of Allen and Giffin,³ Allen and Barker,² and Huffman,¹¹ and by Giffin's summary.⁹ These studies show that most patients aged less than 60 years with polycythemia vera, who are not in an advanced stage of the disease, can safely be given an initial course of phenylhydrazin in 0.1-gm. doses 2 or 3 times daily until a total dosage of from 3 to 4 gm. of the drug has been administered, or, if less than this dosage is required, until definite clinical evidence of active hemolysis presents itself. The drug in such dosage is cumulative in its action and hemolysis almost always continues for a week or 10 days following its withdrawal. During this initial treatment patients should be treated as though they were ambulatory, under hospital observation if possible, and every effort should be made to keep the circula-

* Read by title before the American Society for Clinical Investigation, Atlantic City, New Jersey, May 2, 1932.

tion free and active. On the other hand, phenylhydrazin should be given cautiously, if at all, in cases with advanced arteriosclerosis and visceral lesions, in cases in which the patient is bedridden, in cases in which the history is suggestive of extensive preëxisting thrombosis, and in cases in which patients are aged more than 60 years. In certain such cases rapid hemolysis and fatal outcome¹⁰ have occurred with small dosage.

The immediate problem of this paper is a consideration of the method of treatment best adapted to the control of polycythemia vera following the initial course of treatment. In some of the earlier cases the treatment was omitted completely after the initial course and resumed only when the polycythemic state became marked and symptoms became aggravated. This type of treatment had distinct disadvantages, especially because of the fact that the daily administration of phenylhydrazin requires close observation by the physician, and the patient must look forward to recurring periods of disability. It was recognized that an ideal method of treatment would be one which would maintain the patient in a more nearly normal condition so far as symptoms, erythrocyte count, and blood volume were concerned. By the method of trial and error it was finally found that the administration of from one to three 0.1-gm. doses of phenylhydrazin 1 day of each week, the dosage being varied chiefly according to the symptoms, was usually followed by satisfactory results. To our surprise it also developed that long-continued administration of the drug in this manner was followed in some of the cases by apparent complete inactivity of the disease, so far as the polycythemic state is concerned, with maintenance of normal blood count and blood volume for many months without phenylhydrazin. This has been a striking observation, clinically, in view of the extreme degree of polycythemia vera originally present in these cases. Fluctuation in the degree of polycythemia is a feature of the natural course of erythremia.⁸ Anemia has occurred following gastrointestinal hemorrhage, and anemia with the appearance of immature cells has been described in advanced stages of the disease, but complete remission to normal blood count and normal blood volume with the patient in good health has been thought to be of rare occurrence.

Data on Cases Under Observation from 1925 to 1928. We are reviewing here chiefly the records of those patients with polycythemia vera who were given an initial course of phenylhydrazin under our observation during the years 1925, 1926 and 1927 in order to obtain a conception of the remote effects of treatment. It should be remembered that this was an experimental period, and the experience gained formed the basis for the foregoing and subsequent conclusions; phenylhydrazin was sometimes administered in cases that would now be regarded as unsuitable, and occasionally in excessive dosage.

From January 1, 1925, to January 1, 1928, 37 patients were seen whose condition was diagnosed as polycythemia vera. Of these 25 were given an initial course of treatment by phenylhydrazin hydrochlorid under our immediate observation. Four of the cases in which satisfactory data have been obtainable are presented in the form of brief abstracts. These data exemplify what may be accomplished by the more or less regular administration of small doses of phenylhydrazin over a period of several years. Notes on the remaining cases will be tabulated. Case 1 illustrates control following the initial course of treatment for 4 years by a small dosage 1 day each week. Case 2 illustrates control with a gradual reduction of dosage over a period of 4 years to less than 0.1 gm. each month. Case 3 illustrates absence of increased acquired tolerance to the drug on the recurrence of polycythemia. Case 4 illustrates complete remission without phenylhydrazin after 6 years of regular weekly dosage.

Abstracts of Cases. CASE 1.—A man, aged 50 years, came under our observation January 4, 1926. He had had polycythemia vera for approximately 4 years. He also had a duodenal ulcer. The spleen was moderately enlarged. Erythrocytes numbered 8,390,000 (estimated erythrocytes 8,330,000*); the percentage of erythrocytes by hematocrit was 75; whole blood volume was 205 cc. for each kilogram of body weight, and the viscosity of the blood was 20.6.

The patient was given 3.8 gm. of phenylhydrazin in 0.1-gm. dosage over a period of 18 days. Following this, he was much more active mentally and pain in the legs, troublesome before treatment, was much relieved. At this time, the erythrocytes numbered 4,440,000; the percentage of erythrocytes by hematocrit was 38; whole blood volume was 104 cc. for each kilogram of body weight, and the viscosity of the blood was 4.

After the initial course of treatment the patient was given 0.1 gm. of phenylhydrazin 3 or 4 times each week, with some variation in dosage, over a period of 4 years, during which time the symptoms were under satisfactory control and the erythrocyte counts never returned to their former high levels; they varied from 4,800,000 to 7,100,000, as a rule between 5,000,000 and 6,000,000. Following this, the patient took the drug irregularly, chiefly according to the recurrence of symptoms. After one year of this irregular dosage erythremia again developed, the erythrocytes reaching 8,260,000 in July, 1931. The patient stated at that time, however, that he felt confident from his former experience that he could again bring the condition under control by proper dosage. It is significant, however, in such an advanced case that the high blood volume could be kept under control for 4 years by the systematic weekly administration of small doses of phenylhydrazin.

CASE 2.—A man, aged 59 years, came under our observation April 20, 1927. He complained chiefly of flushed face, intolerance to heat, attacks of mental confusion, and loss of memory, which had existed for 3 years. Albuminuria had been present and an occasional erythrocyte was found in the urine. The concentration of urea in the blood was normal. The spleen was just palpable. Erythrocytes numbered 6,660,000 (estimated erythrocytes 7,220,000); erythrocyte percentage by hematocrit was 65; the whole blood volume was 162 cc. for each kilogram of body weight, and viscosity

* Based on the hematocrit reading compared with a normal of 45 per cent, and 5,000,000 erythrocytes. It assumes that the erythrocytes of polycythemia vera are normal in volume.

of blood was 10.6. The patient was given 3.6 gm. of phenylhydrazin in 0.1-gm. dosage over a period of 12 days. After treatment the erythrocytes numbered 2,290,000, unnecessarily severe anemia having been produced. The percentage of erythrocytes by hematocrit was 27; whole blood volume was 87 cc. for each kilogram of body weight. Superficial thrombosis developed in the legs, but there were no serious sequelæ. There were no symptoms except weakness and slight pain in the feet.

Over a period of 4½ years the erythrocytes were enumerated monthly and careful records were kept of the phenylhydrazin taken. On the patient's recovery from the anemia caused by the initial course of treatment he began taking an average of 2 gm. of the drug each month, approximately 5 doses of 0.1 gm. each week. This amount was gradually decreased until in 1931, 4 years after the first examination, he was taking an average of 0.06 gm. each month. Beginning with May, 1930, the number of doses (0.1 gm.) each month exceeded 2 on only 1 occasion, and since January, 1931, an amount of phenylhydrazin in excess of 0.05 gm. each month was taken on only 2 occasions, when, respectively, 0.15 and 0.2 gm. were taken. In view of this it is probable that the amount of phenylhydrazin taken from May, 1930, to August, 1931, was not sufficient to cause hemolysis, but may have inhibited the production of erythrocytes. The patient's written statement concerning his experience is of special interest: it should be stated that a capsule contained 0.1 gm. of the drug. "It seems to me the tables show that continued administering of phenylhydrazin, gradually and in time reduces the activity of the system in the production of red corpuscles. The tables show that in the 7 months of 1927 after leaving St. Mary's Hospital I took an average of 20½ capsules per month. In 1928, the average capsules taken decreased to 14½ per month; in 1929 to 6½ per month; in 1930 to 3½ per month; and the first 9 months of 1931, an average of only ½ capsule per month. It is true that decreasing dosage did not hold the red count down to the same average and the average of the blood counts increased in 1928, 1929, and 1930, yet the increase is negligible and in 1931, on the other hand, the average count decreases while the average monthly dose of medicine goes down to the least of any of the years." The average number of erythrocytes by monthly counts was 5,650,000 in 1928; 5,880,000, in 1929; 6,260,000, in 1930, and 5,930,000 in 1931.

CASE 3.—A man, aged 50 years, came under our observation June 8, 1927. He complained chiefly of weakness and extreme exhaustion over a period of 2 years.

Erythrocytes numbered 6,810,000 (estimated erythrocytes 8,000,000); the percentage of erythrocytes by hematocrit was 73; the viscosity of the blood was 15, and the blood volume was 246 cc. for each kilogram of body weight. Over a period of 10 days, 4.4 gm. of phenylhydrazin was given, after which the erythrocytes numbered 4,940,000; the viscosity of the blood was 7.5, and the percentage of erythrocytes by hematocrit was 64. During treatment thrombosis of a superficial vein in the left leg developed. At this time, however, marked general improvement had occurred in the symptoms.

On dismissal, the patient was advised to take 3 doses (0.1 gm. each) 1 day a week, but through a misunderstanding he took this dosage 3 times a week. August 11, 1927, erythrocytes had become reduced to 2,400,000; several days previous to this count he had discontinued the use of the drug. October 15, 1927, the erythrocytes had risen to 6,500,000. The patient then took 0.1 gm. of the drug 3 times a week, and the erythrocytes fluctuated from 5,000,000 to 3,000,000 until February 1928. Again, on insufficient dosage, the number of erythrocytes increased to 6,300,000, and the patient took 0.2 gm. daily between April 6 and June 6, 1929, following which they became reduced to 3,500,000. Satisfactory control again was obtained by the administration of 3 or 4 doses a week of 0.1 gm. each until October, 1929,

when the erythrocytes had increased to 7,000,000, but were easily reduced again by an increased dosage of the drug.

The patient was in a satisfactory condition approximately 3 years following the initial course of treatment, although his record indicated that he had not satisfactorily determined the exact regular dosage which would keep his blood under constant control. The concentration of urea in the blood in June, 1928, was 14.4 gm. in each 100 cc. The return of phenol-sulphonaphthalein in the urine was 72 per cent. This was after the patient had been under treatment for 1 year.

CASE 4.—A man, aged 56 years, came under observation August 16, 1927, giving a history indicative of at least 4 years of polycythemia vera.

Erythrocytes numbered 7,040,000 (estimated erythrocytes 7,550,000); the erythrocyte percentage by hematocrit was 68; the whole blood volume was 166 cc. for each kilogram of body weight, and the viscosity of the blood was 13. The spleen was slightly enlarged. Four and six-tenths grams of phenylhydrazin was given in 20 days. After treatment, erythrocytes numbered 4,450,000; erythrocyte percentage by hematocrit was 47; whole blood volume was 125 cc. for each kg. of body weight, and the viscosity of the blood was 5.2. The patient had obtained relief from vertigo, gastric distress, headache, and nervousness. Following the initial course of treatment, 0.2 or 0.3 gm. of phenylhydrazin was taken each week for approximately 9 months from November, 1927. During this time the maximal and minimal number of erythrocytes for each cubic millimeter of blood was 5,920,000 and 4,730,000, respectively. In only 4 of the 9 determinations during this time were the erythrocytes found to exceed 5,500,000 for each cubic millimeter of blood, and at no time did they fall below 4,500,000. The patient was entirely relieved of all symptoms and saw no reason for further reduction of the erythrocytes. There was a period of 2½ months following this during which the patient did not take any phenylhydrazin.

The patient returned for examination July 2, 1928. Erythrocytes numbered 5,030,000; erythrocyte percentage by hematocrit was 59; whole blood volume was 141 cc. for each kilogram of body weight, and the viscosity of the blood was 5.4. The concentration of urea in the blood was normal and a test of hepatic function showed no retention of dye. He had been working regularly and feeling well.

In the next 18 months the patient took from 0.2 to 0.5 gm. of phenylhydrazin each month, an average dose of much less than 0.1 gm. each week, and from ¼ to ½ as much as he had taken previously. During this period, 11 blood counts were made; the erythrocytes varied from 5,370,000 to 4,000,000, and there were no symptoms which seemed to be definitely attributable to polycythemia vera.

The patient was examined April 14, 1930, 2½ years after the original treatment. Erythrocytes numbered 4,560,000; erythrocyte percentage by hematocrit was 55; whole blood volume was 92 cc. for each kilogram of body weight, and the viscosity of the blood was 5.8. There was some complaint of attacks of dizziness; otherwise, the patient felt well and had been working regularly.

From May 12, 1930, to August 27, 1931, a period of 15 months, the patient took almost inconsequential amounts of phenylhydrazin, and for the last 5 months of that period none was taken. Only twice did the erythrocytes exceed 5,000,000. At the present time the patient seems to be entirely relieved of polycythemia vera.

Comment on Abstracted Cases. In all of the abstracted cases response to the initial course of treatment was prompt and satisfactory. In Case 1, the patient, a man, aged 50 years, was able to maintain a satisfactory erythrocyte count, after the initial dosage,

for a period of 4 years on approximately 0.4 gm. of the drug each week. In Case 2, the patient, a man aged 59 years, was able gradually to reduce the dosage from an average of 0.5 gm. each week to 0.1 gm. each month over a period of 4 years; lately, even a smaller amount was taken each month. Finally, there was an absence of the polycythemic state and control of symptoms was completely effected. In Case 3, a man, aged 50 years, the patient's blood was brought under control with somewhat more difficulty than in the average case, but on each elevation of the erythrocyte count above normal there was no greater difficulty in reducing the blood count than was noted at the time of his initial treatment. There also was no evidence of impaired renal function 1 year after treatment was begun. In Case 4, a man, aged 56 years, the patient has never been markedly polycythemic since the initial course of treatment and the polycythemic state has been entirely absent since 1930. This result was obtained with a dosage which was gradually reduced from 0.3 gm. each week to complete withdrawal of the drug in the last five months. There was no evidence of reduced renal or hepatic function 1 year after treatment.

Of the 25 patients who received the initial course of treatment when under our observation, Cases 1 to 7 are reported herewith. The tabulation indicates the use of phenylhydrazin and the ultimate result in the remaining 21 cases.

TABLE 1.

Case.	Age, years, sex.	Comment.
1-4	..	Reported. Excellent control or complete remission.
5	31 F.	Excellent control on 1.3 to 1.6 gm. twice a year. Phenylhydrazin not necessary for the last 1½ years. Total duration 13 years. Patient under treatment 6½ years.
6	55 M.	Excellent control on gradual reduction of dosage from 0.9 gm. each month to 0.9 gm., every 3 months. Normal erythrocyte count last 6 months without phenylhydrazin. Total duration 12 years. Patient under treatment 6 years.
7	55 M.	Excellent control with normal blood count on 0.1 gm. each week. No evidence of renal insufficiency after 5 years of treatment. Slight increase of retention of dye on test of hepatic function after 12 years of splenomegaly and 5 years of treatment. Total duration of disease 13 years. Patient under treatment 6 years.
8	62 M.	Good control on 0.2 gm. weekly. Accidental death 1½ years later. Total duration, 4+ years.
9	56 M.	Fairly good control with 0.2 gm. daily for 5 days each month. Cardiac (?) death 3½ years later. Total duration, 12 years.
10	59 M.	Good control 1½ years later on 0.1 gm. 3 times a week. Drug discontinued because of cerebral thrombosis. Venesections since then. Living in poor health 4½ years later. Total duration, 8 years.
11	25 M.	Good control 4 years later on 0.2 gm. weekly. Treated by various other methods.
12	64 M.	Fairly good control 3 years later. Four courses with total dosage of 4 gm. in each course. Amputation of leg for arterio-sclerotic disease.
13	55 M.	Fairly good control 3 years later. Inadequate treatment. Prostatectomy.

TABLE 1.—(Continued.)

Case.	Age, years, sex.	Comment.
14	62 F.	Inadequate treatment. Death 3 (?) years later.
15	43 M.	Inadequate treatment. Treated by various methods. Death 6 years later. Total duration, 10 years.
16	58 M.	Inadequate treatment. Two courses only. Death 4 years later. Total duration 12 years.
17	56 M.	Inadequate treatment. Death 6 months later. Cause indeterminate.
18	65 M.	Data inadequate. Living 4 years later.
19	67 M.	Drug discontinued because of age and superficial thrombosis. Death 1 year later. Cardiac (?).
20	63 F.	Drug discontinued. Total dosage only 2.6 gm. Death 6 months later; cerebral hemorrhage.
21	56 M.	Drug discontinued. Took only 0.7 gm. Indications of frontal lobe tumor. Death 1 year later.
22	52 F.	Drug discontinued because of nausea and vomiting. Living 5 years later. Immature leukocytes, 5.5 per cent.
23	43 M.	Hypernephroma and polycythemia vera. Initial course of treatment. Venesections later. Recurrence of hypernephroma 4 years later.
24	62 F.	Death under initial course of treatment. Total 4 gm. Severe phlebitis. Total duration 7 years. Case reported elsewhere. ⁹
25	66 F.	Carcinoma of the breast and polycythemia vera. Short pre-operative course only of phenylhydrazin. Death following operation. Case reported elsewhere. ⁹

In 9 of these 21 tabulated cases, on which data are less complete, fairly good or good control of the disease was secured. Hence, in 13 of the 25 cases it would seem that treatment resulted in definite improvement. In 4 cases inadequate treatment was given; these are not included in our study. One case of carcinoma of the breast, 1 of hypernephroma, and 1 of tumor of the frontal lobe can also be discarded from consideration. In 3 cases the drug was discontinued because of the age and general condition of the patient; it had not yet been learned that patients aged more than 60 years, with advanced arteriosclerosis and visceral disease, are likely to react quickly and seriously to phenylhydrazin. Eliminating these 10 cases, thus reducing the number from 25 to 15, in 13 of 15 cases fairly good, good or excellent results were obtained with phenylhydrazin. There was 1 death under treatment; the patient was aged 62 years and had portal thrombophlebitis. This and other fatal cases have been reported by Giffin and Conner. In 1 case, data are entirely inadequate.

Of the 25 patients, 12 died within a period of 6 years; however, eliminating cases of carcinoma of the breast, hypernephroma, cerebral tumor, and 1 accidental death, the number of deaths is 8. Four of these patients were aged more than 60 years when they came under our observation. Only 1 patient aged less than 60 years, who was given adequate treatment had died of the disease; this patient had been ill for at least 12 years.

Of the entire group of 37 patients, 12 were not treated under our immediate observation. The following tabulation indicates the ultimate outcome and treatment in this group:

TABLE 2.—CASES NOT UNDER IMMEDIATE OBSERVATION.

Case.	Age, years, and sex.	Comment.
26	35 F.	Phenylhydrazin. Excellent control followed by complete remission. Treated at home.
27	36 F.	Phenylhydrazin at home with fair control. Splenectomy later. Living 2½ years after operation.
28	38 M.	Phenylhydrazin. Inadequate treatment at home. Fair control. Good health 5 years later.
29	62 M.	Phenylhydrazin at home with relief of symptoms. Death 2 years later from pneumonia.
30	38 F.	Radium treatment; splenectomy. Death following operation. Immature cells in blood.
31	69 F.	Treated by venesection. Fairly good health 5 years later.
32	58 M.	Death 8 months later; cause indeterminate.
33	57 M.	Surgical case; no record of treatment.
34	59 M.	No record of treatment; not traced.
35	58 F.	Inoperable hypernephroma and polycythemia; not traced.
36	54 M.	Treated at home; not traced.
37	45 F.	Treated at home; not traced.

Only 4 of 8 patients treated at home, to our knowledge, were given phenylhydrazin. Excellent control followed by complete remission for 2 years without administration of the drug was reported in 1 of these 4 cases. The patient was a woman, aged 35 years, who came under our observation August 20, 1926. For 2 years after the initial course of treatment the polycythemic state recurred at intervals, but was easily controlled by a short course of the drug. There was no evidence of increased tolerance. A report dated April 15, 1931, stated that the patient had not taken phenylhydrazin for 2 years and the blood count had remained within normal limits. She was working regularly as a teacher and did not complain of symptoms which could be attributed to polycythemia vera. The condition of the other 3 patients was fairly well controlled, but the treatment was apparently inadequate.

Data on Cases Under Observation from 1912 to 1919. Usually it is stated in the literature that death occurs in cases of polycythemia vera within 6 or 8 years. It is very difficult in a disease of this character, in which the history of onset frequently is indefinite, to determine the exact duration of the disease. In order to obtain a more definite idea of prognosis we have reviewed the cases of polycythemia vera observed at The Mayo Clinic between the years 1912 and 1919 inclusive. In 14 cases the diagnosis was definite.

We have obtained information concerning 12 of these. Death occurred shortly after decompression for increased intracranial pressure in 1 of the 12. Necropsy disclosed enlargement of the pituitary gland which was due to distention of the vascular channels. Of the 11 remaining patients, 9 died subsequently. Two were living at the time of the last report, 10 and 13 years, respectively, after they had been first examined, the total duration of disease having been 15 and 13 years, respectively. The average length of the disease of the 9 patients who died was 10 years; this average would be slightly increased by the elimination of 1 patient who had been ill for only 3 years. The records of these patients seem to show that probably the onset of the disease in every instance was somewhat earlier than was indicated, so that a total duration of 10 years undoubtedly is a conservative estimate. It can be stated, therefore, that this small group of cases indicates a longer duration of disease than that which usually is reported in the literature. In this period the patients were treated by means of radium, Roentgen rays, and venesection. The records were also reviewed for evidence of cyclic phenomena; fluctuations in the degree of erythrocytosis occurred, but whether there had been actual remissions in the course of the disease could not be determined. However, there were no positive data in the records to indicate complete remissions accompanied by normal health, and one would infer that the prolonged remissions observed following the administration of phenylhydrazin are not a natural feature of the disease.

The Toxicity of Phenylhydrazin Hydrochlorid. There has been a great deal of discussion in the literature concerning the toxic effect of phenylhydrazin hydrochlorid on the liver and kidneys. Many drugs, however, are harmful in large dosage and therefore a consideration of dosage is of special importance. Stealy¹⁵ reported a case of polycythemia vera in which treatment with phenylhydrazin had been given for 3 years; during this time there was no clinical or laboratory evidence of deranged hepatic or renal function.* In 3 of our cases, blood urea estimations and urinalysis were normal after 5 years, 1 year, and 1 year, respectively, of initial treatment. In 1 case the dye test for hepatic function was normal after 1 year of active treatment. In 1 case retention of dye was graded 1, 5 years after the institution of treatment of a man, aged 64 years, with a total duration of disease of at least 12 years. Allen and Giffin have shown that dogs receiving 1.26 gm. of phenylhydrazin for each kg. of body weight in 146 divided doses over a period of 8 months, did not excrete abnormal urine, and had normal blood urea and normal excretion of phenolsulphonephthalein at the end of that period; significant retention of the dye on test for hepatic function.

* In a paper published after completion of this article, Stealy records his observations on this case over a period of 7½ years; there was no evidence of damage to hepatic or renal function (Polycythemia Vera. J. Am. Med. Assn., 1932, 98, 1714).

was not apparent. Allen and Barker studied the organs of 2 of the 3 animals used in these experiments; they found that the livers of these animals were essentially normal and that there was no abnormality of the kidneys which could be attributed to phenylhydrazin. They also found that the kidneys and livers of animals given an amount of phenylhydrazin daily sufficient to cause death on the 5th day, manifested only atrophy of the parenchymal cells of the liver and overloading of the convoluted tubules of the kidneys with iron. It seems to be conclusive that the relatively small dosage necessary for the control of polycythemia vera in man is not harmful to renal and hepatic function in the absence of advanced visceral or vascular disease. Moreover, in our experience examination of the blood films morphologically during treatment has not revealed marked toxic abnormalities of leukocytes. However, it is most important to recognize that clinical experience has shown that phenylhydrazin in small dosage may cause rapid hemolysis and fatal outcome among older patients with advanced visceral disease. Whether this is due entirely to hemolysis with its sudden temporary increase in the nitrogenous products of the blood, or partly also to some special toxicity, has not been determined. This aspect of treatment has been considered by Giffin and Conner.

Tolerance to Phenylhydrazin Hydrochlorid. Our experience with the administration of phenylhydrazin hydrochlorid to human beings does not indicate that an abnormal tolerance to the drug develops. In every instance when the erythrocyte count has become abnormally high after treatment with phenylhydrazin, readministration of the drug was followed by satisfactory reduction of erythrocytes. It is true that after the production of anemia with phenylhydrazin the administration of more of the drug does not decrease the erythrocytes proportionately, but the conclusion concerning tolerance should be based either on a normal or increased number of erythrocytes. Bratley, *et al.*,⁴ have recently concluded that anemic rabbits and dogs acquire tolerance to the drug; but it appears that they have not taken into account the significance of the low erythrocyte level at the beginning of their experiments. The chief requirement for experimental work bearing on the question of clinical tolerance is that the erythrocytes should be at the same or similar levels in all experiments. It would be expected that more of the drug would be necessary to reduce the erythrocytes from 3,000,000 to 2,000,000, than from 5,000,000 to 4,000,000, but this would not be regarded as evidence in favor of increased tolerance because regeneration is more active when the count is low. Experiments of the authors indicated that if an animal is given daily 12 mg. of the drug for each kg. of body weight, the number of erythrocytes drops approximately 1,500,000 cells and then maintains a level on continuance of the same dosage. This does not indicate increased tolerance but more active regeneration; however, if the number of erythrocytes is

allowed to return to normal the same amount of the drug will have the same effect on the number of erythrocytes.

Miscellaneous Considerations. In 2 cases of the series of 37, immature cells of the granular series appeared in the blood in appreciable numbers, presenting a morphologic picture similar to that of chronic myelogenous leukemia. In 1 of these cases phenylhydrazin had not been given; in the other, the drug was discontinued because it produced nausea and vomiting. In both of these cases immature cells appeared late in the course of the disease and constituted only 5 or 6 per cent of the leukocytes. In none of the cases in which phenylhydrazin was used, even in larger amounts and over prolonged periods, did immature cells appear, although marked leukocytosis was common. Myelocytes were sometimes present at the time of first examination, but these disappeared following treatment.

It should be assumed that polycythemia vera will result fatally usually within 10 or 15 years from the time of onset. Treatment may logically be directed to maintenance of reduced blood volume on the theory that this may delay the advancement of vascular and visceral disease. Phenylhydrazin will safely reduce the blood volume if patients are not too old or in a too advanced stage of the disease, but should be administered with great caution or not at all to old, or debilitated patients. During the initial course of treatment the patients are best treated in hospital on an ambulatory regimen in order to keep the circulation free and decrease the likelihood of venous thrombosis. An initial hemolysis can usually be produced by the administration of 0.1 gm. of phenylhydrazin 2 or 3 times a day until a total of from 3 to 4 gm. has been given. Occasionally resistant cases will be found which require a larger total dosage. In these cases it has been our practice to discontinue the drug after 3 gm. has been given because of the cumulative effect, and if necessary to resume treatment in a few days giving additional total dosage of 1 gm. in each subsequent series, repeating this procedure until a proper degree of hemolysis has been obtained. An active preparation of phenylhydrazin must be obtained and it should be freshly placed in capsules each week as needed.

After the initial course of treatment, and within a few weeks at most, phenylhydrazin should be given in 0.1-gm. doses 3 or 4 times a week or in sufficient dosage to maintain the erythrocyte level between 5 and 6 millions. Our patients are now instructed to take from 0.2 to 0.4 gm. each Wednesday and to have the erythrocytes counted regularly, at least once a month. They are warned against increasing or decreasing the dosage too much or withdrawing the drug without careful consideration; these instructions prevent extreme swings in erythrocyte count and blood volume. Complete remissions have occurred on this regimen, but cases have not been observed long enough to decide whether life will be prolonged.

Summary. The experience with 37 patients with polycythemia vera, who were observed from 4 to 6 years, shows conclusively that after the initial course of phenylhydrazin has been satisfactorily completed, the disease frequently can be controlled by the administration of a very small dose (0.1 to 0.4 gm.) of the drug each week. This control in some instances has been accomplished by a dosage which has been shown to be ineffective experimentally so far as hemolysis is concerned (for example, 0.06 gm. a month); this fact leads one to suspect that phenylhydrazin may have another effect on the blood picture such as an inhibitory effect on the production of erythrocytes, although it is fairly well proved to have a stimulating effect on the production of leukocytes. This suspicion cannot at present be proved but is worthy of further consideration. Some of the patients after from 2 or 4 years of treatment have been able to dispense with the drug entirely and maintain a normal number of erythrocytes. Other patients have found it necessary to use the drug regularly; in some instances subsequent courses of daily dosage have been necessary. The occurrence of complete remission in some of the cases is apparently of especial significance. The untoward effects of phenylhydrazin are also considered; this phase of the subject has been amplified in a paper by Giffin and Conner. Phenylhydrazin should not be given if the diagnosis of polycythemia vera, with increased blood volume, cannot be well established (see McNamara and Sansum¹³).

NOTE.—Cases 1, 8, 12, 13, 15, 16 and 17 of this study are cases 4, 1, 5, 6, 3, 7 and 2, respectively, of the report of Brown and Giffin.⁵ Case 7 of this study is the case reported by Allen.¹ Cases 24 and 25 of this study are cases 3 and 4, respectively, in the report of Giffin and Conner.¹⁰

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A DISCUSSION OF THE RÔLE OF ARTERIAL THROMBOSIS IN THE VISCERAL DISEASES OF MIDDLE LIFE, BASED UPON ANALOGIES DRAWN FROM CORONARY THROMBOSIS.*

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THE views of the writer would perhaps be more accurately indicated if the title of the paper had been phrased in interrogatory form, for it is his purpose in discussing the subject rather to inquire what may be the part played by arterial thrombosis in the viscera than to affirm what that rôle is. Only in the case of the heart and the brain have we anything approaching satisfactory information concerning the incidence and significance of arterial thrombosis. With respect to the other organs (pancreas, spleen, kidneys, intestines, liver, lungs) our knowledge is surprisingly scanty, concerning both the pathologic and the clinical aspects of such thrombosis. For this reason much of the discussion which follows must unfortunately be hypothetical in character and based upon analogies rather than on actual observations. But that arterial thrombosis plays a rôle of some importance in the diseases of viscera other than the heart and brain, and that the subject has hitherto received surprisingly little attention, cannot be doubted.

The steady growth in our knowledge concerning disease of the coronary arteries has established a number of important facts which it is desirable to review because of the bearing they may have upon disease of the arteries in other viscera: (1) The great frequency of coronary arteriosclerosis in the middle and later years of life; (2) the lack of any close relationship between coronary and peripheral arteriosclerosis; (3) the surprisingly early age at which coronary artery disease often manifests itself; (4) the frequent existence of coronary disease without preëxisting arterial hypertension; (5) the

* Presented at a meeting of the Association of American Physicians, Atlantic City, May 3, 1932.

importance and frequency of thrombosis in the course of coronary arteriosclerosis.

Evidence as to the validity of the above statements may be summarized as follows: The great frequency of coronary arteriosclerosis in the middle years of life is shown both by every-day clinical experience and by postmortem findings. In persons of over 40 years of age heart disease is much the greatest single cause of death, and among the causes of heart disease in such persons coronary artery disease easily stands first.

The conception of arteriosclerosis as a "general" process has been so widely accepted that we have almost lost sight of the fact that the process is notoriously irregular in its distribution and that there is little or no relationship between the state of the arteries in the heart or the other viscera and that of the peripheral arteries. The relative independence of visceral and peripheral arteriosclerosis has been emphasized by Fitz,¹ by Romberg² and by many others.

Recent statistics concerning coronary artery disease have made it clear that such disease is very common in early middle life. In an analysis of 287 cases of coronary thrombosis (Conner and Holt³) it was shown that in 75 per cent of the patients the symptoms appeared before the age of 61 years and in 33 per cent before the age of 51 years. In this connection it is well to recall that Romberg² many years ago insisted that we must regard arteriosclerosis, not as a disease of old age ("Alterskrankheit"), but rather as a process of wearing out ("Abnutzungskrankheit"), and that this wearing-out process may begin very much earlier in certain structures or organs than in others.

The frequent occurrence of coronary thrombosis without pre-existing hypertension has been clearly shown by the figures of Parkinson and Bedford,⁴ Levine,⁵ and Conner and Holt;³ and it seems safe to say that at the most not more than half of the cases of coronary artery disease are associated with arterial hypertension. In their recent study of 500 cases of angina pectoris White and Bland⁶ found that only in 36 per cent of the cases was there an associated arterial hypertension.

As to the importance and frequency of the complication of thrombosis in coronary arteriosclerosis there can be no question, although accurate statistical figures are not available. Not only does thrombosis supervene in a large proportion of the cases of angina pectoris, but even more frequently do the symptoms of the attack of coronary closure give the first and only intimation that serious coronary disease exists. We have learned during recent years that most attacks of coronary thrombosis are not immediately fatal and that the occurrence of 2 or more such attacks in the same individual is the rule rather than the exception.

Relation of Arterial Thrombosis to Arteriosclerosis. With the growing appreciation of the vast clinical importance of coronary throm-

bosis the question is being asked more and more whether the atherosclerotic changes in the vessel wall are the chief causal factor or whether there are other factors, such as changes in the character of the blood itself, which play an important rôle. Unfortunately the question cannot be answered at present. There are various reasons for thinking that other factors may play a part in the production of thrombosis, but upon the evidence at present available we are forced to believe that atherosclerotic changes in the arterial wall are an essential, and probably are the chief, prerequisite for the formation of the thrombus.

Having discussed the more important facts concerning disease of the arteries of the heart, the question arises as to how far these facts can be applied to the arteries of other viscera. Is there evidence to show that arteriosclerosis is common in the other viscera in the middle years of life, and if so, is thrombosis the frequent result of such sclerosis that we know it to be in the case of the coronary arteries?

All the evidence at hand indicates that the tendency to atherosclerotic change, which is so marked a feature in the heart in middle life, is shared by most of the other viscera. We know that such changes are very common in the kidneys, in the brain, in branches of the mesenteric arteries. We know that they are not infrequent in the arteries of the pancreas and the spleen and, under certain special conditions, even in the branches of the pulmonary arteries; but we know very little concerning the occurrence of *thrombosis* in the diseased arteries of most of these viscera. Only in the case of the brain is the clinical diagnosis of arterial thrombosis made with any frequency, and even with this organ there is often a hesitancy about making the diagnosis if the patient be one in early middle life. Yet if sclerosis be at all common in the arteries of the various viscera, it is hard to believe that thrombosis is not a frequent complication of such arteriosclerosis.

The question of thrombosis is, we know, closely linked with that of *infarction*, for it is infarction which gives rise to most of the symptoms resulting from thrombosis. Indeed without some infarction it is doubtful if the clinical diagnosis of thrombosis is ever possible. Whether or not infarction results is determined chiefly by the character of the arterial branching and the scarcity or abundance of anastomoses; but in the case of most of the viscera infarction is known to occur from arterial closure due to embolism.

So while, as has been said, we know comparatively little about the actual occurrence of thrombosis, with or without infarction, in the viscera other than the heart and brain, it is difficult to believe that arteriosclerosis, which is known to be common in the other viscera, can proceed without the frequent occurrence of thrombosis. Moreover, in kidneys which are the seat of arteriosclerotic changes it is a common experience to see one or more depressed surface

scars which can best be explained on the basis of an infarct from an old thrombotic closure; one occasionally sees similar depressed scars on the surface of the spleen without anything in the patient's history to suggest that such an old infarct has had an embolic origin.

If, however, the analogy between the heart and the other viscera hold, and if thrombosis in disease of the arteries of these viscera be of frequent occurrence, why is it that the diagnosis of such thrombosis is rarely or never made, whereas the diagnosis of coronary thrombosis is made so frequently and so easily?

The answer lies in part, no doubt, in the special characteristics of the heart itself which favor the making of such a diagnosis. Thrombosis of a coronary artery frequently leads to early death and to the prompt confirmation of the diagnosis. The peculiar features of the pain and certain other symptoms are much more pathognomonic than in the case of other viscera, the electrocardiogram is usually characteristic, and the heart is so accessible to physical examination that the physical signs are often helpful; whereas in the case of the other organs the conditions for diagnosis are much less favorable. Since the cases are probably rarely fatal, confirmation of the diagnosis by autopsy will be lacking, and, in the case of the abdominal viscera, the pain and the disturbances of function are likely to be much less characteristic and helpful. Moreover, most of the other organs are much more liable to other acute diseases which may simulate infarction and confuse the diagnosis.

But that is not the whole answer. One reason for our failure to recognize thrombosis in the arteries of the other viscera lies, I think, in the fact that we fail to have the possibility in mind and so have failed to develop diagnostic criteria.

Is it beyond reasonable hope that such criteria may be developed? I believe not. Twenty years ago coronary thrombosis was hardly more than a pathological curiosity. Repeatedly in the older literature one finds statements indicating that its clinical diagnosis can hardly be expected. In the writings of two recent great clinicians, Osler and Mackenzie, a clear understanding of the clinical picture of this condition is entirely lacking, whereas now there is hardly a disease in the whole realm of internal medicine which can be recognized so promptly and so certainly. With the development of its diagnostic signs we have in turn come to know much more concerning its natural history and have learned to recognize its milder and more benign aspects. May we not expect, after what has happened in the case of coronary thrombosis, that when we begin to look for the signs of thrombosis in the arteries of the kidneys, the spleen, the pancreas and the mesentery, we shall gradually develop criteria which will ultimately make such diagnoses possible?

Let us now consider in how far it may be possible to construct a framework of diagnosis for thrombosis of the arteries of these viscera. For this purpose we have material from two different sources: (1) The symptoms known to result from thrombosis and infarction in the heart; (2) those which result from the infarction which follows the lodgment of emboli in various organs. Thus infarction in the kidneys, spleen, brain and lungs is frequently recognizable, and that in the gastrointestinal tract occasionally so. But the diagnosis is rarely made unless there is reasonably certain knowledge of the existence of conditions which would provide a source for such emboli. In the case of such organs as the pancreas, the liver, the thyroid gland and the uterus we are without this aid from embolic infarction.

In attempting to construct theoretically a framework of diagnostic symptoms for arterial thrombosis in other viscera from analogy with the symptoms of coronary thrombosis, there are two which seem applicable to any organ in which thrombosis is accompanied by infarction. These are *fever* and *leukocytosis*. Both of these are presumably the result of the reactive inflammation excited by the presence of the infarct, and it seems reasonable to expect that they would be present in the case of infarction in any other organ. The other general symptoms, such as shock, pallor, sweating, vomiting and a fall in blood pressure, we might expect to be less pronounced and striking in the case of other viscera than in thrombosis and infarction in the heart. In regard to other symptoms, such as pain and disturbances of function, these would, of course, vary with the individual organs involved. It seems probable that the time relationship between the onset of pain and that of fever may have some diagnostic significance, since the pain should *precede* the fever by an interval of at least some hours.

Let us turn now to a brief consideration of the probable diagnostic features of arterial thrombosis in the several organs.

Kidney. We know fairly well what might be expected in the way of symptoms of thrombosis in the kidney from those which arise as the result of embolic infarction in that organ, and it is very surprising, in view of the frequency with which evidences of old infarcts are seen in arteriosclerotic kidneys, that the clinical diagnosis of arterial thrombosis should be rarely, if ever, made. This must be chiefly because the possibility of such thrombosis is not held in mind. In a person of arteriosclerotic age in whom there is no ground for expecting the discharge of arterial emboli, the occurrence of dull pain and tenderness in the flank, of more or less fever and leukocytosis, and of red cells and albumin in the urine (if absent previously) would seem to justify such a diagnosis.

Spleen. Postmortem evidences of old healed infarcts in the spleens of persons who show no source for arterial emboli suggest that such infarcts are the result of arterial thrombosis. The

symptoms of embolic infarction of this organ are usually so distinct that infarction due to thrombosis should be recognizable if only its possibility were kept in mind. Pain of the pleural type, fever, leukocytosis, tenderness and perhaps muscular rigidity in the splenic region, and not infrequently a to-and-fro perisplenic friction sound over some part of the splenic area, make a sufficiently distinctive picture to warrant the diagnosis of arterial thrombosis, if there is nothing to justify the suspicion of embolic infarction and if other satisfactory explanations of the symptoms are lacking. Thrombotic infarction seems especially prone to occur in spleens which are the seat of massive enlargement, of whatever nature, and in the presence of splenomegaly the possibility of such infarction should be constantly remembered.

Pancreas. Very little is known concerning either arterial thrombosis or arterial embolism in the pancreas. A search of both the pathologic and the clinical literature has yielded surprisingly little information upon this subject. The arteries of the pancreas are frequently the seat of arteriosclerosis.* Most of the arterial branches to the pancreas arise from the splenic artery, which is notoriously prone to extensive arteriosclerotic change, and there seems every reason to expect that the sharply angled branches supplying the pancreas should sometimes be the seat of thrombosis. If thrombosis and infarction occur, nothing is known as to their clinical features. One would expect to find pain of greater or less severity in the epigastric or umbilical regions, with perhaps some tenderness, some degree of shock, some fever and leukocytosis and probably nausea and vomiting—all symptoms which, it must be confessed, might well be evoked by disturbances in various other organs in that neighborhood. If, however, in a person of appropriate age there were the simultaneous appearance of sugar in the urine, that fact would go far toward justifying the diagnosis of arterial thrombosis. For a long time it has seemed to me that some of the abruptly appearing glycosurias in arteriosclerotic subjects might well be the result of pancreatic thrombosis and infarction.

The Mesentery. Infarctions of the gastrointestinal tract are not rare, and the more massive forms are sometimes recognized clinically, although much more often the diagnosis is made first at operation or at the autopsy table. In the large series of cases analyzed by Trotter,⁸ a clinical diagnosis was rare. As infarction may result from arterial embolism and from thrombosis of the mesenteric veins as well as from arterial thrombosis, even when the diagnosis of mesenteric infarction seems justified, it is difficult to be sure that the cause of the infarction is arterial thrombosis.

That arteriosclerosis is common in the mesenteric arteries is

* In Brooks' study⁷ of visceral arteriosclerosis the pancreas is listed as fourth in the order of frequency of arterial disease, following the heart, brain and kidneys.

thoroughly established (Ortner,⁹ Zesas,¹⁰ Sauv  ,¹¹ Lagane¹²), and there seems reason to believe that thrombosis, especially of the smaller arterial branches, is of much more frequent occurrence than is its clinical recognition. In this connection Trotter⁸ comments as follows: "Two circumstances have been responsible for the failure in recognition of the disease; in the first place the clinical picture is extremely variable and in most cases very incomplete, and in the second place the condition has been regarded as so uncommon that it has frequently not even been considered."

As is the case in most other organs, closure of a mesenteric artery or one of its branches does not always result in infarction, and in the absence of infarction we can hardly expect that the arterial thrombosis will be manifest clinically.* Whether or not infarction occurs depends upon several factors: the size of the arterial branch occluded, the state of the venous circulation, the degree of distention or emptiness of the gut, and perhaps individual variations in the arterial anastomoses. It is well known that infarction occurs very much more frequently in the area of gut supplied by the superior mesenteric artery than in that supplied by the inferior.

It is to be expected that the symptoms of intestinal infarction, from whatever cause, would show great variations in character and severity, depending upon the size and the location of the area of gut involved. The clinical picture is usually divided into two stages, with at first symptoms due to irritation of the gut and later with those due to paralysis. At the onset there is violent crampy pain, nausea and vomiting, sometimes diarrhea, and usually prostration, collapse and sweating. The vomitus is often blood-stained, and the stools frequently contain blood. After a day or two, and often after a temporary cessation of the severe pain, the symptoms of paralytic ileus appear—with complete obstipation, great distention, persistent vomiting, pain and tenderness. Among the recorded cases the temperature has been variable, usually elevated, but sometimes normal or subnormal. It seems probable, however, that some degree of fever and leukocytosis must be present in every case at some stage.

Even if the diagnosis of intestinal infarction seems justified, there is still the problem of distinguishing between the three possible sets of causes—mesenteric venous thrombosis, arterial embolism and arterial thrombosis. If, however, it is possible to exclude the usual sources of an arterial embolus and such conditions in the abdomen as predispose to thrombosis in the branches of the portal vein (appendicitis and other severe intestinal inflammations, hepatic cirrhosis, thrombosis of portal veins, etc.) and if the patient be one

* In Trotter's large compilation⁸ thrombosis of the superior mesenteric artery is believed to have occurred in 61 cases. Among these hemorrhagic infarction was found in 34, hemorrhages or intense engorgement in 12, mucous catarrh in 1 and no changes in the intestines in 3. In the remaining 11 cases the patient either recovered or died without autopsy.

in middle life there would be a strong presumption that the infarction was the result of arterial thrombosis.

The recognition of thrombosis of branches of the hepatic artery in the liver and of the bronchial arteries in the lungs is made extremely difficult by the fact that in each of these organs the double vascular supply so reduces the likelihood of infarction from such thrombosis that its occurrence is almost unknown. The same is true of the two centrally placed organs, the thyroid gland and the uterus, which have an arterial supply from each side of the body. In the case of large fibromyomata of the uterus, however, arterial thrombosis is known to occur and to result in areas of necrosis and softening which may give rise to severe symptoms.

It is recognized, of course, that such a theoretical discussion of the diagnosis of arterial thrombosis and infarction in the abdominal organs may prove to be in certain respects quite inaccurate, and these suggestions are offered merely in the hope that they will serve to direct attention to a subject which must have some clinical significance and which hitherto has been given little consideration. Everyone knows how common it is to encounter obscure, acute illnesses marked by more or less abdominal pain, fever and prostration, in which no diagnosis can be ventured. Some of these may well belong to the group under consideration. One of the chief difficulties in the working out of such a clinical picture is the fact that only rarely will it be possible to get prompt postmortem information in suspected cases, as such attacks in the abdominal viscera must usually result in recovery. If we are ever to gain further knowledge, this must come from the combined efforts of the clinician and the pathologist. At the present time the pathologist is as lax in searching for arterial lesions in the abdominal viscera as is the internist in seeking for their signs during life. The publication of the clinical reports of even a very few cases of arterial thrombosis in the spleen, pancreas, or kidneys with postmortem confirmation would inevitably excite interest in the subject and would result, I believe, in the steady accumulation of facts which ultimately would place the clinical diagnosis of such lesions upon a firm basis.

Summary. Attention is called to the fact that whereas thrombosis in the arteries of the heart and of the brain is known to be common and is easy of clinical recognition, almost nothing is known concerning the symptoms of arterial thrombosis in the abdominal viscera. Nevertheless the frequent occurrence of degenerative changes in the arteries of the pancreas, kidneys, spleen and mesentery indicate that thrombosis in these vessels cannot be rare.

The failure to recognize attacks of arterial thrombosis in the abdominal organs must be due in part to the inherent difficulties of diagnosis, but is almost certainly also due partly to our failure to have the possibility of such attacks in mind and to have accumulated pertinent evidence.

An attempt is made to construct a framework of diagnosis for arterial thrombosis in the kidney, pancreas, spleen and mesentery by utilizing certain symptoms associated with thrombotic infarction in the heart (fever, leukocytosis) and those which result from infarction due to embolism in the kidney, spleen and mesentery.

It seems probable that when both internists and pathologists begin seriously to seek for evidences of such thromboses and to correlate their findings, the difficulties of diagnosis will be found to be not insurmountable, and the lineaments of the respective clinical pictures will gradually emerge from the present obscurity, much as have those of the diagnosis of coronary thrombosis.

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FAMILIAL EOSINOPHILIA.

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THIS report details the study of four families in each of which several members exhibited a distinct, persisting and unexplained eosinophilia. The term familial is used to indicate the presence of eosinophilia in several members of a family, in whom none of the known causes of eosinophilia could be found, such as allergic states, dermatoses and parasitic infestations, especially trichinosis. A few authors have used the designation "constitutional eosinophilia"

to refer to this condition, whether familial or in but one member of a family.

The terms constitutional eosinophilia and familial eosinophilia seem to have been used synonymously. The latter, however, has been adopted for use here as being more descriptive and having been the first in use.

In spite of the fact that as early as 1911 Klinkert¹ called attention to familial eosinophilia, its importance seems to have been neglected. So few examples can be found in the literature that one can only guess as to its frequency. Klinkert's report described a family of 6 with eosinophil counts varying from 7 to 15 per cent. However, in this family there seemed to be an adequate explanation of the eosinophilia, for 3 of 5 children exhibited allergic manifestations in the form of asthma, angioneurotic edema and urticaria. I have previously noted eosinophilia in 3 generations of the family of a patient with eosinophilic leukocytosis and Hodgkin's disease.² Allergic factors were present in all 3 generations.

The family incidence of allergy and of transmissible parasitic disease doubtless accounts for some of the eosinophilias that have been classified as familial or constitutional. Under the title of familial eosinophilia in this paper, however, are grouped only those families in which all of the usually accepted causes of eosinophilia have been excluded, according to our present methods of investigation. In the remaining literature cited, the possibility of allergic eosinophilia and its other causes have been excluded. Such a family was reported by Gaugain,³ in which the mother had an eosinophilia of 19 per cent, and 3 children, 10, 14 and 15 per cent, respectively. The most completely studied example of familial eosinophilia was published by Armand-Delille, Hurst and Sorapure.⁴ The patient, a boy aged 8 years, had an eosinophilia of between 51 and 62 per cent. Three sisters and a brother had eosinophil counts of 14, 21, 27 and 27 per cent, respectively, and the father, 7 per cent. All of the usual causes of eosinophilia were carefully excluded. Similar instances under the designation of constitutional eosinophilia are reported by Bastai,⁵ Cirio,⁶ Spiro and Pfanner,⁷ Smits,⁸ Lucas⁹ and Cattaneo.¹⁰ Fanton¹¹ spoke of "so-called eosinophil diathesis" in recording eosinophilia in a father and daughter with no allergic history.

In Chart I are summarized the eosinophil percentages in 6 families reported in the medical literature.

The opportunity to investigate 4 families with eosinophilia has been afforded during the past year. In each instance the patient, through whom attention was attracted to the family, had been on the Medical Service of Dr. Stengel in this hospital.

Report of Cases. CASE 1.—E. P., a girl, aged 18 years, was admitted on November 24, 1930, because of severe cough. For 2 years there had been symptoms suggesting pulmonary infection—increasing cough, dysp-

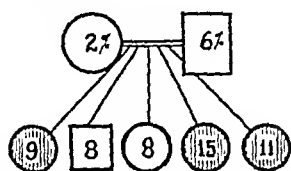
nea, purulent sputa, chest pains, irregular fever and loss of weight. At times there were severe attacks of diarrhea and generalized abdominal pain.

Physical Examination. The patient was greatly emaciated. Examination of the chest, which was of a phthisic configuration, revealed signs of extensive infiltration of the lungs with cavities at both apices. Tenderness was complained of over the colon, and a mass could be palpated in the region of the cecum. There was no enlargement of the spleen or lymph nodes.

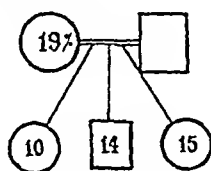
Laboratory Data. The red blood count showed a moderate secondary anemia, averaging 4,200,000 cells, with a hemoglobin content of 60 per cent (Sahli). The leukocyte count remained elevated, at a fairly constant level of 20,000 cells, with a persistent eosinophilia which, at times, reached 32 per cent.

CHART I.—SIX FAMILIES WITH FAMILIAL EOSINOPHILIA.

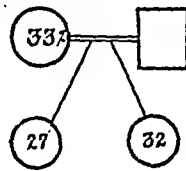
Klinkert-1911.



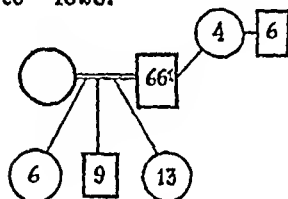
Gauguin-1914.



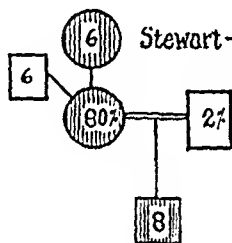
Bastai-1923.



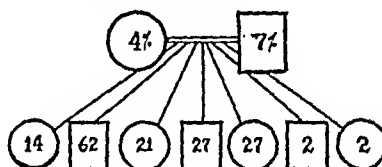
Cirio-1926.



Stewart-1929.



Armand-Delille-1930.



In this and subsequent charts the presence of allergic manifestations is indicated by cross-hatching. The circles represent females and the squares males. The figures within the circles indicate the percentage of eosinophilia.

The sputum was loaded with tubercle bacilli. Repeated stool examinations were negative for ova and parasites, but contained large numbers of tubercle bacilli. Skin tests, using the usual antigens of inhalants and foods, disclosed no abnormal skin sensitivity. A tuberculin test was not done. Roentgen rays of the chest revealed extensive tuberculosis of both lungs with multiple cavities. No calcifications of cysts of trichinosis were seen in the thoracic musculature.

In brief, the patient suffered from a florid type of pulmonary and probably enteric tuberculosis. There was neither personal nor family history of allergy. The patient stated specifically that she had not been allowed to eat pork in any form for several years, had had no past illness suggestive of trichinosis, and had received no medication which might have induced eosinophilia. There was no history of skin disease.

Comment on Case 1. Tuberculosis was suggested as a possible cause of eosinophilia. It has been reported in infantile tuberculosis by Belloni.¹² Brumlik and Sikl,¹³ and Cordier, Croizat and Carle¹⁴ recorded cases of eosinophilia in lymph node tuberculosis, and Grass and Simmert¹⁵ noted eosinophilia as an index of allergy in

tuberculosis. Kilduffe¹⁶ mentioned its occurrence in active tuberculosis. However, when other members of this patient's family were studied, it was found that eosinophilia was present in all of its members, and tuberculosis in none. Therefore this possibility, as the cause of the eosinophilia in this family, seemed improbable. In Chart II are the blood counts made on the patient and her various relatives, as far as the family tree could be traced.

The outstanding features of the data charted are the marked increase in the absolute number of eosinophils in each of the 8 relatives studied and the occurrence of eosinophilia on both the father's and mother's side of the family (the average normal for absolute numbers of eosinophils quoted by Clough¹⁷ is 250 cells per c.mm.). There was no family relationship between the father and mother before marriage. This very unusual finding of eosinophilia in both branches of the family, in the absence of personal and family history of allergy, seemed to cast some doubt on the thought that trichinosis and other parasitic infestations had been excluded. However, in none could a history of trichinosis be obtained. A letter from Dr. J. D. Boger, Health Officer for the City of Lebanon, Pa., where all the family lived, stated that no cases of trichinosis had been seen in that vicinity or reported to the Board of Health during the past 4 years. Stool studies for ova and parasites, which could be done only on the immediate members of the family, were all negative. According to the present clinical methods for determining trichinosis, it was excluded in this family.

Lastly, blood counts were repeated on the immediate family 4 months later, and the absolute numbers of eosinophils coincided closely with the figures recorded in Chart II.

CASE 2.—J. L., a boy, aged 12 years, was studied in the Cardiac Section of the Medical Clinic of this hospital on March 7, 1931. He had no special complaints, but was referred by the school physician because he had had "rheumatism" 2 years ago, and rheumatic pains in the left leg 1 year ago. Occasionally he experienced mild precordial pain. There was a history of the usual childhood diseases, including otitis media, but not chorea or scarlet fever. No personal or family history of allergy, skin disease or trichinosis could be elicited.

Physical Examination. The patient was well developed, in a good state of nutrition and had no fever. No evidence of cardiac disease was found, and there was nothing abnormal in the physical examination, except slight pallor of the conjunctivæ and mucous membranes.

Laboratory Data. The erythrocyte count averaged 3,000,000 cells with a hemoglobin content of 60 per cent (Sahli). The leukocyte count was 6000 with 22 per cent eosinophils. No ova or parasites were found in stool examinations. Roentgen rays of the muscles of the shoulder girdle gave no evidence of calcification of trichinal cysts. Here again the persistent eosinophilia seemed an extraneous finding.

Comment on Case 2. It was thought that a low-grade chronic infection, related to the rheumatic pains, and perhaps the moderate secondary anemia, might play a rôle in the causation of the eosino-

CHART II.—EOSINOPHILIA OF FAMILY P.

Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. P. Mother	44	85	8,000	57	18	5	20	1600	None.
Mr. P. Father	50	97	8,500	57	24	2	17	1445	None.
Ed. P. Daughter	18	55	12,000	60	8	..	32	3840	None.
El. P. Daughter	12	88	8,400	50	20	2	28	2352	None.
I. P. Father's bro.	54	87	9,200	62	21	2	15	1380	None.
J. R. Mother's bro.	55	111	7,500	54	22	2	22	1650	None.
E. F. Mother's sis.	53	100	7,200	66	18	1	15	1080	None.
E. R. Mother's bro.	46	92	8,200	72	13	..	15	1230	None.

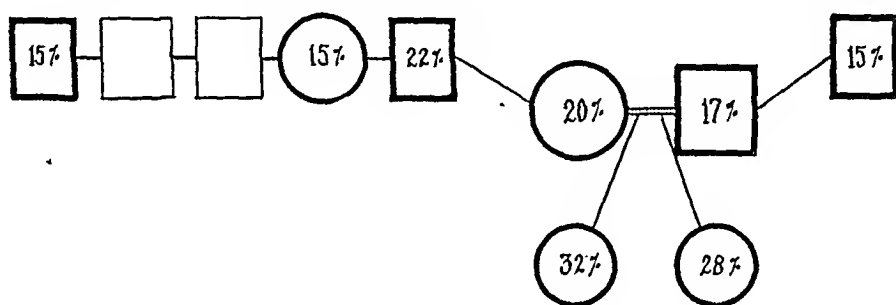
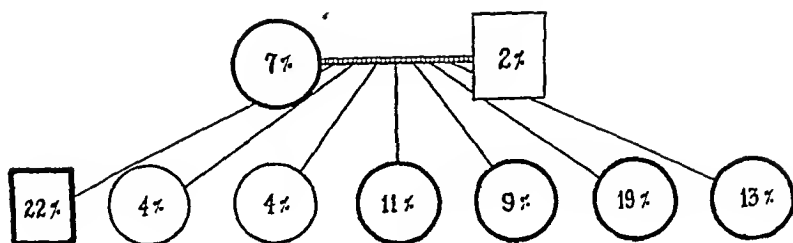


CHART III.—EOSINOPHILIA OF FAMILY L.

Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. L. Mother	36	80	8,600	67	25	1	7	602	None.
Mr. L. Father	39	101	5,000	50	45	3	2	100	None.
J. L. Son	12	60	6,000	48	28	2	22	1320	None.
A. L. Daughter	14	83	8,600	59	35	2	4	344	None.
E. L. Daughter	10	80	8,000	70	26	..	4	320	None.
M. L. Daughter	8	75	9,000	51	34	4	11	990	None.
R. L. Daughter	6	69	7,600	52	35	4	9	684	None.
Ja. L. Daughter	3	61	10,000	56	23	2	19	1900	None.
P. L. Daughter	3	63	9,000	59	24	4	13	1170	None



philia. Such a relationship has been described by Akerren,¹⁸ Fiedler¹⁹ and others, and, indeed, several cases of rheumatoid arthritis with myositis and persistent eosinophilia have recently been studied in this hospital. The coincidence of postinfectious anemia with eosinophilia has been noted by Tallqvist²⁰ and Beifeld and Barnes.²¹ Indeed, these explanations were accepted for lack of any better one, until a marked eosinophilia was discovered in other members of this family, whose counts are summarized in Chart III.

Each of the 9 members of the family, except the father, had absolute eosinophil counts above the average normal. All except the patient were quite healthy people, although the 4 sisters had moderate hypochromic anemia. There was no evidence of tuberculosis or chronic infection, and stool studies in each member of the family were negative for ova and parasites. One year later complete blood counts were repeated on every member of the family. The percentages of eosinophilia were essentially unchanged, with the exception of E. L. who previously had 4 per cent (320 eosinophils) and after 1 year had 10 per cent, with a leukocyte count of 8600. The anemia noted in the 4 sisters was not present when the second counts were taken.

CASE 3.—T. M., a boy, aged 3 years, was treated in this hospital because of lobar pneumonia. Recovery was uneventful. At the age of 2 years he had been treated here for poor nutrition, secondary anemia and septic tonsils. At that time the blood showed a leukocytosis of from 10 to 18,000 with an eosinophilia reaching as high as 50 per cent. The eosinophilia was present on the second admission, but disappeared completely during the acute stage of pneumonia, to return again to its previous level after convalescence. Otherwise he was an entirely average child in good nutrition and with a slight secondary anemia. There was no personal or family history of allergy, trichinosis or skin disease.

Laboratory Data. Repeated stool studies were negative for ova and parasites. The red blood count averaged 4,300,000 cells, the hemoglobin 75 per cent (Sahli) and the leukocyte count 15,000, with 42 per cent of eosinophils. All other laboratory tests were negative.

Comment on Case 3. Here again, as in Case 2, is represented a patient with chronic infection (septic tonsils), secondary anemia and eosinophilia. The other members of the family exhibiting increased numbers of eosinophils were quite healthy people, but there was found also a slight hypochromic anemia. Examination of the feces gave no evidence of infestation in any member of the family, and all the known factors which might be related to eosinophilia were ruled out.

CASE 4.—J. B., a man, aged 38 years, had been admitted several times to the Medical Service of this hospital because of severe asthma of 5 years' duration. Asthma began 2 days after thyroidectomy. It seemed to be of an infectious type, being associated with pansinusitis, but was unrelieved by any medical or surgical procedures. There was no history of allergy in any other member of the family.

Physical Examination. The patient was in a good state of nutrition. Slight cyanosis, polypoid degeneration in the nose with purulent sinus discharge, emphysema and typical lung signs of bronchial asthma were the only positive findings. Between attacks he felt entirely well.

Laboratory Data. Repeated stool examinations were negative for ova and parasites. The red blood count averaged 5,000,000 cells with 95 per cent hemoglobin (Sahli). The leukocyte count remained quite constantly at 12,000 cells, with a persistent eosinophilia as indicated in Chart V.

CHART IV.—EOSINOPHILIA OF FAMILY M.

Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mr. M. Father	34	96	7,600	61	33	4	2	152	None.
Mrs. M. Mother	26	80	6,000	51	39	4	6	360	None.
A. M. Daughter	5	70	10,000	58	29	3	10	1000	None.
T. M. Son	3	66	15,000	26	30	2	42	6300	None.
M. M. Daughter	1	70	10,000	57	29	4	10	1000	None.

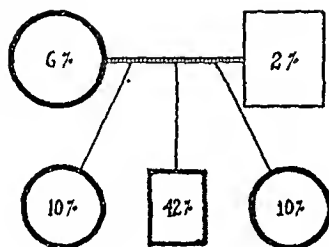
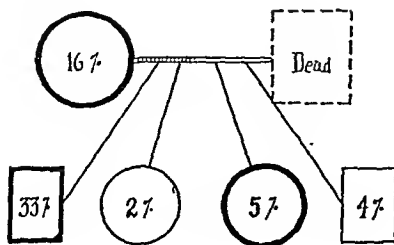


CHART V.—EOSINOPHILIA OF FAMILY B.

Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. B. Mother	69	..	8,000	57	24	3	16	1280	None.
J. B. Son	38	90	10,300	42	20	5	33	3399	Asthma.
E. B. Son	41	..	8,500	67	22	7	4	340	None.
G. B. Daughter	8,300	67	23	5	5	415	None.
M. B. Daughter	8,200	70	23	5	2	164	None.
Mr. B. Father (dead)	None.



Comment on Case 4. Although the mother had 16 per cent of eosinophils and a daughter 5 per cent, there was no indication of

any personal or family history of allergy, and parasitic infestation was ruled against by negative stool studies.

The unusual feature in this case was the excessive eosinophilic leukocytosis associated with asthma. Moderate eosinophilia is quite common, averaging from 3 to 7 per cent, with a normal leukocyte count, but there are only a few cases on record with eosinophilic leukocytosis of high degree. Herrick,²² in 1911, reported a case with 77 per cent and a leukocytosis of 57,000 cells. Armand-Delille,²³ in 1927, described a case of asthma with a leukocyte count of 35,000 and 76 per cent eosinophils. It would be of interest to know if, in such cases, the excessively high eosinophilia might have been caused by an allergic state added to a preëxisting familial eosinophilia, as might well be suggested in this case.

Discussion. Every effort has been made to rule out the known causes of eosinophilia in the 4 families described. Transmission of the allergic state through several generations is quite commonly encountered; and, since eosinophilia is so closely related to allergy, the question is raised if eosinophilia without allergy, whatever its initial cause may be, may not be transmitted directly from one generation of a family to another. A review of the charts certainly suggests such an hereditary transmission of eosinophilia. According to clinical methods it seems fair to assume that allergic factors have been excluded. The possibility of trichinosis was more difficult to rule out. It is stated that the eosinophilia following trichinosis may last for years, but that it rarely lasts as long as 6 months. Blood counts were repeated after 1 year in 3 of these 4 families, and no essential change was noted in the percentages of eosinophilia. Both Klinkert and Armand-Delille emphasized the fact that eosinophilia in their cases persisted for many years.

Investigations have been exhausted in the effort to prove that trichinosis is not in any way related to the families reported—in the absence of history of any signs or symptoms of trichinal infestation, in the persistence of eosinophilia, by the negative Roentgen ray of muscle for trichinal cysts, and because of its presence in a few very young members of the families who, by reason of their ages, had never included pork in their dietary.

Skin diseases, specific blood disorders and chronic infections have been excluded in these families. In brief, the 4 families discussed in this paper present eosinophilia coincidentally in most of their members, clinically quite independent of any of the known causes of eosinophilia, and have been classified as examples of familial eosinophilia.

Summary. The term "familial eosinophilia" has been used by certain authors to connote eosinophilia in a family, whether caused by allergy, parasites or dermatoses, and by others to indicate its occurrence in families quite independent of a known cause. The latter usage has been adopted in this paper in classifying four

reports of familial eosinophilia. In conclusion, it may only be said that the significance of such an eosinophilia is as undetermined as the nature of the eosinophil, and at present one may only speculate upon an hereditary transmission.

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VASCULAR CRISES.*

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THE term vascular crises is applied to sudden changes in the caliber of bloodvessels resulting either from contraction or from dilatation and causing transitory symptoms through malfunction or nonfunction of the part supplied by the affected vessel. Such crises are conditioned on the activity in the walls of the vessels of a nervous mechanism and in the medulla oblongata of a vasomotor center highly sensitive to reflex and direct stimulation.

The arteries of the body are normally in a state of tonus from which they change in either direction as conditions demand. Such changes constitute one of the important means the body has of adapting itself to the environment: heat produces dilatation, cold contraction of the vessels; during digestion more blood flows through

* Read by invitation before the Evanston Branch of the Chicago Medical Society, April 7, 1932.

the gastrointestinal tract and during exercise the muscles become hyperemic. Psychic influences also play an important rôle in the distribution of the blood—embarrassment leads to blushing, fear and distress produce pallor. In conditions of disease the same phenomena occur, only to an exaggerated degree. In a chill the surface vessels are strangled, the blood is driven back into the center of the body.

The nerves that supply the bloodvessels with constrictor and dilator fibers are of sympathetic origin. The nerve endings fuse with the unstriated muscle cells in the middle coat of the vessels. Nearly all the bloodvessels of the body are supplied with such sympathetic fibers, except perhaps the arteries of the brain which, according to Bayliss,¹ have no vasomotor nerves running in their sheaths. More recent authors, however, especially Forbes and Wolff and Pender,² have shown that even the cerebral vessels are under the control of a nervous vasomotor mechanism, although this is probably less important than the general blood pressure as a regulator of the circulation in the brain.

It is usually held that the vasomotor nerves, barring a few special territories, are largely constrictor in action, that is, their stimulation either at the periphery or through the center in the medulla causes contraction of the vessels. It is highly probable that certain hormones act in the nature of vascular stimulants. The best known of these hormones is adrenalin. Another one may be the mysterious sympathin recently discovered by Cannon.

Dilatation of the bloodvessels has by many been looked upon as a passive process resulting from inhibition of the vasoconstrictor mechanism, but there is considerable proof that dilatation may be at times active. In animals dilatation of the bloodvessels can be produced through stimulation of the central end of the depressor nerve after all vasoconstrictor fibers have been severed. Such an experiment would imply the existence of a vasodilator center, but the convincing experiment applicable to man is still lacking.

General Vascular Crises. Vascular crises are general or local. General crises are exemplified by the sudden rises of blood pressure, so often seen in persons who are already hypertensive. The rise may be due to toxic, psychic or other causes and may pass off without any untoward symptoms. Frequently, however, such sudden general crises produce headache, dizziness, aphasia, monoplegia, hemiplegia, hemianopsia and even convulsions. It is at times difficult to determine whether the symptoms are the result of the high blood pressure crisis or whether some functional or anatomic change in certain brain territories precedes and causes the rise in blood pressure. The relation of these general crises to angina pectoris has recently been studied by Lewis, but while often accompanied or followed by anginal seizures, the sudden increase of blood pressure may not be the only factor.

Dilatational crises manifest themselves in a sudden fall of the blood pressure. In practice it is often difficult to decide how much of the fall of the blood pressure is due to vascular dilatation and how much to cardiac weakness. For example, in sudden coronary obstruction, in acute dilatation of the heart, in cardiac rupture there is a tremendous fall of blood pressure from direct depression of the cardiac function. The symptoms of dilatational crises closely resemble those of severe hemorrhage. They are pallor, sweating, sighing respiration, dizziness, thready pulse and at times unconsciousness. The condition is well exemplified by surgical shock. It is possible that some toxic agent such as histamin may play a rôle in the production of these symptoms.

Very marked shocklike crises occur at times in Addison's disease, probably as the result of a vasomotor paralysis or of vasodilatory stimulation or of both. Aside from true Addison's disease there is a functional adrenal depression,³ which is also accompanied by a fall in blood pressure but less profound than that of true Addison's disease.

Local Vascular Crises. I shall now leave the subject of general vascular crises and consider local crises which possess a peculiar clinical interest of their own. In the majority of instances these crises are of spastic type and result from a constriction of the vessels. Such a constriction, I have already explained, is usually brought about through the mediation of the vasoconstrictor mechanism. It is quite possible, however, that contraction of the vessels can occur independently of the sympathetic nervous system. All the arteries and arterioles, even those of the brain in which the question of a vasomotor nerve supply is still perhaps not absolutely settled, have well-marked muscular coats and can undergo an intrinsic or myogenic contraction. The problem is similar to that confronting us in the heart. Here, too, we have a myogenic contraction, but one distinctly influenced by nerve impulses of extrinsic origin.*

Whatever the results of spastic contraction of vessels may be, they depend upon a variety of factors—the size of the vessel occluded, the duration of the spasm, the previous state of nutrition of the part and the possibilities of prompt collateral circulation. I once saw the pulse disappear completely at the wrist for a brief period through spasm of the radial artery without any noticeable after-effect. If the circulation is cut off for a sufficiently long time either functional or organic changes take place in the starved territory. Until recently the opinion prevailed that these results

* As is well known, one of the pioneers in the study of vascular crises is Professor Pal of Vienna. A few years ago I happened to be acting as Exchange Professor in the Peter Bent Brigham Hospital in Boston and on one of my morning ward rounds I had occasion to demonstrate a case illustrating vascular crises. During the course of my remarks I referred to Pal's work. At the end of the discussion, Dr. Christian introduced me to an elderly gentleman who had been one of my auditors—it was Professor Pal.

depended upon cutting off of the total blood supply, *i. e.*, of the nutritive material, but Barcroft and others have shown that the local deprivation of oxygen, for which I have proposed the term *histanoxia*,* is very damaging to the tissues.

Local vascular crises can occur in almost any organ or part of the body. The affected vessels may be normal, at least in appearance; often, however, they are the seat of varying degrees of arteriosclerosis. When not too rigid, diseased arteries are more sensitive to vasomotor influences than normal vessels. This accounts for the greater frequency of spasticity in such vessels. While they respond more readily to nervous and other influences, they return to their previous state more slowly than healthy vessels. Arteries subject to abnormally high blood pressure seem to be especially sensitive to vasoconstrictor influences.

Vascular Crises in the Brain. On account of the multiplicity of functions centered in the brain, vascular crises present a more varied picture than the same processes in other organs of the body. Monoplegia, hemiplegia, aphasia and convulsions are some of the possible motor crises. They occur most frequently in persons with hypertension, but they can also occur in those whose blood pressure is not markedly abnormal.

A number of years ago I was asked to see in consultation an elderly lady who had been seized suddenly and without warning with right-sided hemiplegia. Her daughter had arranged to go to Europe on a Government mission and wanted to know whether it was safe for her to leave her mother. During my examination I tested sensation with a pin and as I proceeded upward from the toes the patient suddenly exclaimed, "Oh, Doctor, I can move my foot; now my leg." Before I left the house the motion had completely returned in the paralyzed parts. The surprised patient credited me with superhuman powers. It is difficult to explain such a case on anything but a temporary angiospasm. The persistence of slight anatomic changes does not of necessity imply that the underlying cause was not a spasm, that it was a hemorrhage or a thrombosis. It is conceivable that highly irritable vessels might remain in a state of protracted spasm, which would lead to degeneration of the brain tissue.

It is a common error to consider convulsions in an individual of middle life who is not a true epileptic as uremic. This latter diagnosis is apparently strengthened by the finding of albumin in the urine immediately after the convulsive seizure. In many cases, however, there is between attacks no evidence either in the blood or in the urine of serious renal damage, so that it seems unlikely that the convulsions are due to uremia, whatever that mysterious

* From *ιστός*, tissue; *ἀνάξια*, without oxygen. The word *anoxemia* sometimes used for local oxygen starvation connotes rather a general state of the blood than a local condition.

condition may be. The patient usually has a single convulsion at the time, but the attacks tend to repeat themselves at irregular intervals. The majority of patients in whom such convulsions occur are long-time sufferers from hypertension. The attacks, as a rule, pass off without any aftermath, although occasionally there is a transitory disturbance of vision, perhaps of speech or of mentality. I am inclined to believe that these attacks are of vascular origin due to a general hypertensive crisis. To distinguish them from true epilepsy, the term *epilepsia tarda* or *senile epilepsy* has been applied to the condition.⁴ In treatment, the best results are obtained by free bleeding from the arm. Uremia and eclampsia are very similar to *epilepsia tarda* and may also represent vascular crises. The same thing applies to lead encephalopathy. There is, of course, something back of the vascular spasm, whether we are dealing with eclampsia, uremia or *epilepsia tarda*. There is some basic provocative agent, but whatever it is, it acts apparently not directly on the brain cells but on the circulation in the brain.

In addition to motor manifestations we meet with various sensory and psychic disturbances such as dizziness, tinnitus, hemianopsia, quadrant anopsia, amaurosis and headache. The so-called migraine headache has many features that suggest that it is an angiospastic condition. At times a spasm of the homolateral temporal artery is observable. What causes the spasm however is unknown—heredity, toxins, allergy, epileptic analogies crowd into the picture. Fundus and visual field studies during the attacks are desirable.

There are also evanescent psychic and psychomotor disturbances that are best explained on an angiospastic basis—sensory aphasia, amnesia, brief psychotic outbursts, etc.

Vascular Crises Affecting the Eye. These are quite common. I have already referred to their occurrence in migraine and in convulsions, but they may also occur independently. Redslob,⁵ of Strasbourg, attributes retinal spasm to humoral causes, to changes in the ion concentration. His experiments seem to show that high concentration contracts and low concentration dilates the retinal vessels. Spasm is likely to be bilateral and lead to amaurosis. Barré⁶ has described a syndrome characterized by vertigo, headache, paracousia and vasomotor phenomena of the head, which he attributes to pressure upon the sympathetic nerves by arthritic changes of the cervical vertebræ.

Vascular Crises in the Lungs. These undoubtedly occur, but we know little about them; at least we know little of vascular spasm in the lung. Vascular dilatation is an accompaniment of all acute inflammatory processes. There is, however, a condition, acute pulmonary edema, in which a vascular factor is highly probable. It is met with most often in hypertensive states, also in myocardial weakness and in mitral stenosis, and occasionally immediately after tapping the chest. This last variety usually follows too rapid

removal of a large amount of fluid in cases of hydrothorax of long standing. It seems to be brought about by a sudden rush of blood into the compressed lung, the altered vessels of which are not able to hold back the plasma. The patient may die, drowning as it were in his own juices.*

The pulmonary edema of hypertension or myocardial disease is usually attributed to a sudden weakness of the left ventricle. That, however, is not a complete explanation. I have seen pulmonary edema occurring simultaneously with a marked rise of general blood pressure and all the evidence of a powerfully acting left ventricle. It seems to me that there must be some change in the tonus of the pulmonary vessels, a sudden dilatation analogous to that of post-aspirational edema. Clinically the most striking features of acute pulmonary edema are intense dyspnea, *angor animi* not inferior to that of angina pectoris, an abundance of moist râles all over the chest and the expectoration, not invariably, of quantities of frothy fluid which on boiling coagulates completely.

The treatment is most satisfactory if promptly carried out. Three measures, separately or combined, rarely fail to bring the patient back from what looks like the brink of the grave—hypodermic injection of morphin and atropin, venesection and dry cupping of the chest. The last measure whatever its *modus operandi* is a procedure of indisputable value.

Vascular Crises in the Heart. Are the vessels of the heart liable to vasomotor spasm? This question opens up the endlessly discussed subject of the nature of angina pectoris. At the risk of being challenged, but as a means of saving space and time, I will say at once that I am a believer in the coronary origin of angina pectoris. It is scarcely necessary to speak to this audience of disease of the coronary arteries. Through the work of Herrick, Sutton and Le Count the subject is well known in Chicago. The angiospastic theory of angina pectoris seems to me to account best for the clinical picture and for the results of medicinal and surgical treatment. Slight sclerotic changes in the coronary arteries and in the aortic sinus render the cardiac vessels more irritable.

Vascular Crises in the Abdomen. Vascular spasm analogous to that at the basis of angina pectoris may occur in the abdomen, as pointed out by Ortner and by Osler. I have seen it in an interesting case: An elderly man came to me complaining of pain in the legs on walking a short distance. If he stopped, the pain passed off and he could walk without further trouble. The condition was clearly one of intermittent claudication. There was also a mild, readily controlled diabetes. After a year or two typical seizures of angina pectoris supervened. These eventually ceased entirely. Instead, the patient began to have sharp pains in the midepigastrie

* This type of edema has been called edema by recoil.⁷

region for which no digestive error or other gastric cause could be found. From their character I attributed them to spasm of branches of the celiac axis. But that was not all. One day he noticed a peculiar disturbance of vision—in certain directions objects were blurred. A careful study of the visual fields revealed the existence of a quadrant anopsia.

The gastric crises of locomotor ataxia and the colic of lead poisoning have been attributed by a number of writers to angiospasm. I do not believe that this is the whole explanation, however. There must be some direct disturbance of the gastrointestinal canal to account for the constipation in lead colic and for the almost uncontrollable vomiting in tabetic crises.

Vascular Crises in the Lower Extremities. A few moments ago I referred incidentally to *intermittent claudication* which was so well described nearly 80 years ago by Charcot. While its essence is sclerosis of the arteries of the leg, it is probable that, in addition to the organic narrowing, there is a transient vasomotor spasm. The patient can walk only a short distance before the attack comes on, but if he waits a few moments the pain and numbness pass off and he is able to continue his walk with ease. Many patients with intermittent claudication have flat feet, practically all are heavy smokers; nearly 50 per cent of those affected are Russian Jews. Allen and Brown⁸ found intermittent claudication to be an inaugural symptom of thromboangiitis obliterans. Of 200 cases one-half were Russian Jews, the other 100 being made up of a great variety of races, including native American. It is interesting that while in intermittent claudication arteriosclerosis is the rule, it is the exception in true angiitis obliterans. The diagnosis of intermittent claudication is easily made by the history and by finding absent pulsation in the dorsalis pedis and in the posterior tibial arteries. Roentgen ray examination reveals calcification along the course of the vessels; many patients, as I have said, have flat feet. The importance of recognizing it is that false diagnoses are often made, such as sciatica. One should, however, bear in mind the fact that bilateral sciatica is practically never sciatica. Diabetic neuritis may simulate intermittent claudication. Flat feet, metatarsalgia and rheumatism are some of the other diagnoses made. The prognosis depends largely upon the degree of angiospasm. The more spasm and the less sclerosis, the better the prognosis. Complete recovery is possible with proper treatment, but it must be borne in mind that intermittent claudication may be the forerunner of that horrible disease, thromboangiitis obliterans. In thromboangiitis (Buerger's disease) there is so much structural change in the arteries and veins that any considerable angiospasm is scarcely possible. However, it probably plays an intermittent rôle in those vessels in which occlusion by thrombosis has not proceeded too far.

Raynaud's Disease. Raynaud's disease is primarily an angiospastic affection. Not all cases so called are Raynaud's disease. Studies of the circulation, the effect of sympathectomy and anatomic investigations all indicate that the closure of the vessels is not due to endarteritis but to vasoconstriction. The cause of this constriction is unknown—endocrine imbalance, toxins, cold are some of the factors suggested. The disease is symmetrical and passes through stages of pallor and cyanosis with numbness and aching in the syncopal or pallid stage, and may end in peripheral gangrene.

Scleroderma is in part also an angiospastic condition; it is frequently accompanied or preceded by typical Raynaud's phenomena. But there must be a special element in scleroderma to account for the profound trophic changes that occur not only in the extremities but often in the face and chest. In a doctor's wife under my care at the present time not only are the extremities involved but the skin of the upper part of the chest and over the clavicles is becoming so tightly adherent that the patient cannot fully extend the neck. I may add that as far as my own experience is concerned, sympathectomy confers no permanent benefit; Adson has seen good results from ganglionectomy combined with sympathectomy; Leriche has recently advocated parathyroidectomy. The patient mentioned above is at present in Strasbourg for this operation.*

A local crisis of obscure nature is the so-called acrocyanosis, a bluish or reddish discoloration of the hands and feet. It is not like the asphyxial stage of Raynaud's disease for it persists, especially in cold weather. In all probability there is an angiospasm which reduces the capillary flow through the skin. There is no pain and there are no trophic changes.

A local *vasodilator* disturbance in the extremities is the condition known as *erythromelalgia* (Weir Mitchell's disease). The characteristic features of this are intermittent attacks of vasodilatation involving the hands and feet and associated with severe burning. During the attack the parts are red, hot, flushed, the veins dilated and throbbing.¹⁰ Cold water and elevation give relief. A disturbance resembling erythromelalgia may appear as an early symptom of *polycythemia rubra*.¹¹

The Cause of Pain in Angiospasm. Sir Thomas Lewis explains the pain in the extremities in intermittent claudication on the basis of an accumulation of metabolites. These metabolites or tissue poisons, the products of muscular activity, accumulate within the muscles and irritate the fibers directly, not however to the point of producing a muscular cramp. Lewis's experiments, simple but well planned, appear to support this view, but his interpretation does not seem to me to fit all cases of vascular occlusion. A sudden

* Longcope⁹ has called attention to the occurrence of hypoglycemia in scleroderma.

thrombosis of a vein such as occurs in phlebitis is accompanied by instantaneous violent pain as if the individual had been hit with a brick. It seems hardly likely that the pain could be so prompt in onset and so severe in character if it were due to metabolites, for the accumulation of metabolites must take time. Furthermore, the sudden plugging of an artery, which does not interfere with the return flow through the veins, is usually also very painful. It is possible that in such cases the pain is produced by a sudden stretching of the artery proximal to the obstruction. This would bring the pain into analogy with biliary and ureteral colic.

Another argument in favor of an additional or a different interpretation than that given by Sir Thomas Lewis is found in the case of infarction. In certain organs, such as the spleen and kidney, acute thrombosis or embolism leading to infarction is often accompanied by violent pain and shock. In the case of renal infarcts I have seen the diagnosis of appendicitis made. The question of metabolites hardly enters in such cases.

I have under my care a patient with polycythemia rubra. Some time ago he was suddenly seized with agonizing pain in the left testicle. Upon examination I found what seemed to be a thrombosis of the veins. Subsequently he had a similar attack about the ankle, a sudden violent pain with redness and swelling, evidently also a thrombotic occlusion. In the case of the testicle the formation of metabolites is not likely to play an important rôle.

The conclusion seems warranted that the causes of pain in vascular occlusion, whether from spasm or plugging, are multiple:

1. The accumulation of toxic metabolites in active tissues, especially muscles.

2. Histanoxia, ischemia or local anoxemia.

3. Pressure upon sensory nerve endings in the walls of vessels either through stretching proximal to the obstruction or through an actual squeezing of the nerve endings during spasm. In both cases there would also result an inadequate blood supply to the vessel itself and to the surrounding receptor organs.*

Treatment of Vascular Crises. General angiospastic crises with rise of blood pressure are best treated by vasodilators such as nitroglycerin, erythrol tetranitrate, perhaps the choline derivatives, or by free bleeding. Rest, mental and physical, and good action of the bowels are also necessary.

Local Crises. The attempt must be made to relax the spasm. This can be accomplished by local heat, hot baths and by diathermy. Certain drugs have a value such as the nitrites, derivatives of cho-

* How the afferent impulses obtain cortical registration as pain is not definitely settled. In the case of the periphery of the body they may travel upward with the somatic nerves; in the case of the viscera that avenue is out of question. Afferent impulses from the heart course centrally largely by way of the pathways going to the first and second segments of the thoracic spinal cord.¹²

line, chloral hydrate and luminal; atropin, papaverin or morphin and atropin also may be used.

In severe cases affecting the extremities certain special measures may be indicated—the injection of foreign proteins such as typhoid bacilli or sympathectomy or ganglionectomy.

Vascular Dilator Crises. General dilator crises must be treated by rest, lowering the head and by vasomotor stimulants—adrenalin, pituitrin, ephedrin, strychnin, digitalis, caffen or coffee, or by transfusion of blood or by continuous venous infusion of glucose-salt solution.

In certain circulatory conditions in the lower extremities it is important from the standpoint of treatment to determine whether the condition is dependent upon the mechanical plugging of the vessel or upon vascular spasm. Scott and Morton¹³ have proposed a test by means of which it is possible, except in the case of Raynaud's disease, to make this distinction. They find that general or spinal anesthesia, or local anesthesia produced by the injection of 1 per cent solution of procain, provokes a vascular dilatation with a consequent increase in surface temperature. If the defect in circulation is due to organic obstruction the local hyperthermia does not occur, but it does occur if the obstruction is due to angiospasm. A number of other tests have been designed to aid in differentiation and in planning treatment in cases of vascular obstruction of the lower extremities; for example, the histamin test and the triple cuff method of Pearse and Morton¹⁴ determine the point to which the vessels are patulous.¹⁵

Thrombosis and Embolism. I have thought it proper to include under the general heading of vascular crises a few words about thrombosis and embolism which, though they are different phenomena, may produce a very similar clinical picture. The recent medical literature has much to say about the apparent increase in frequency of thrombosis and embolism. Most of the relevant literature comes from surgeons and pathologists who concern themselves chiefly with thrombosis and embolism in the lungs and limbs; but the clinician of mature years knows that thrombosis of the coronary arteries is increasing, whatever may be true of thrombosis elsewhere. Improvement in diagnosis is not the whole explanation. The increasing stress and strain of life is a most important factor; it certainly plays a part in the striking mortality of medical men from coronary disease. Diabetes, as Nathanson¹⁶ has shown, is also a powerful factor in the production of sclerosis of the coronary arteries.

Embolic crises are common in the cerebral vessels. They may occur whenever any source of emboli exists in the body, such as venous thrombosis and subacute and vegetative endocarditis. But the process is especially common in mitral stenosis. Whenever I see a patient under 40 years who has suddenly had a hemiplegia

or a monoplegia, I first look for the cause in the heart. Naturally there are other possibilities, such as syphilis and hemorrhage, but in my experience I have found hemiplegia under 40 years most commonly due to mitral stenosis. The patient may not know that he has heart disease nor may there be a murmur when he is first examined because the murmur of mitral stenosis is fugitive. But whether the murmur is present or not, in nearly all cases there is a loud, snappy first sound that is highly suggestive of mitral stenosis.

While the symptoms of cerebral embolism may pass off in a few hours just as those of angiospasm, if they last longer than 24 hours they are apt to be more or less permanent. Furthermore, embolism in mitral stenosis is likely to recur. Both of these points are important to bear in mind in giving a prognosis. Embolism of the central artery of the retina is unfortunately a common condition occurring in the same circumstances in which we find cerebral embolism. A picture similar to embolism in the brain can be produced by cerebral thrombosis. While, however, in embolism the symptoms are sudden in onset, without any warning, in cerebral thrombosis there are often premonitory disturbances such as vertigo, headache and perhaps transient aphasia or weakness of a limb before the complete picture of hemiplegia appears. Improvement is very common in cases of thrombosis because the thrombus shrinks or becomes channeled and the circulation is in whole or in part reestablished. Perhaps there is also a spasm in the vessels which recedes after a time.

Thrombosis and embolism are common in the lungs especially after operations and in chronic valvular and muscular heart disease. Postoperative pulmonary embolism from dislodgement of a clot in the operative field is usually a fatal catastrophe, although lately a few successful operations following the pioneer and courageous efforts of Trendelenburg have been reported.

Mesenteric thrombosis is not a very common vascular crisis. Prompt surgical treatment seems to be the only chance in the average type of case. The causes are obscure. Thrombosis and embolism of the extremities are frequent conditions—in arteriosclerosis, after operations, during the course of acute infections, in myocardial and valvular heart disease.

In the coronary vessels thrombosis is common and, as I have said, definitely on the increase. The results are variable. There may be instantaneous death, a lingering painful death, pain with subsequent congestive heart failure, or pain of variable duration with apparently full recovery. Other sequelæ such as rupture of the heart and cardiac aneurysm need not concern us now.

In conclusion I wish to say that there is much yet to be learned both clinically and experimentally about the bloodvessels and their important and somewhat neglected share in the circulation of the blood.

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THE ACCUMULATION OF IRON IN TUBERCULOUS AREAS.

III. EFFECT OF FERRIC CHLORID INJECTIONS ON THE COURSE OF DEVELOPMENT OF TUBERCULOSIS IN RABBITS.*†

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TWENTY years ago P. A. Lewis demonstrated that trypan red injected into the subcutaneous tissues of rabbits penetrated readily into caseous areas of tubercles in the lungs.¹ Similar observations with methylene blue were made on guinea pigs by DeWitt.² In previous communications^{3,4} it has been shown that a vital dye (trypan blue) or iron in the form of its salt, ferric chlorid, when injected into the blood stream rapidly accumulates into an area of inflammation, where the substance is fixed and fails to drain to the tributary lymph nodes. Subsequent experiments^{5,6} demonstrated that repeated daily intravenous injections of ferric chlorid in rabbits were followed by an accumulation of iron in tuberculous areas of the lungs. The iron was shown to accumulate in the caseous areas of tubercles. These experiments suggested that the accumulation of iron into tuberculous areas might alter the character or course of development of the disease. In a series of 16 rabbits inoculated with a bovine strain of tubercle bacilli repeated intra-

* Read before the American Association of Pathologists and Bacteriologists, April 29, 1932, Philadelphia.

† This study was aided by a grant from the William W. Wellington Memorial Research Fund.

venous injections of 0.25 per cent ferric chlorid for about 10 weeks were followed by a definite prolongation of the survival time of experimental animals. The animals increased in weight during part of the period of these injections. Both control and experimental animals died of generalized tuberculosis.

The present series of experiments were undertaken to determine first, whether the administration of quantities of ferric chlorid larger than had formerly been used and over a longer period would enhance the previous results on the increased survival time of tuberculous rabbits, and, in the second place, to obtain information on the effect of ferric chlorid injections on the development of the tuberculous lesion.

Experimental Method. Bovine tuberculosis was induced in weighed rabbits by the intravenous injection of a diluted saline suspension of a Ravenel strain. Twenty-seven days later the animals were divided into two groups. One group was kept to serve as control. Intravenous injections of 0.25 per cent ferric chlorid were started in the other group as follows: 1 cc. on the first day, 2 cc. on each of the 2 following consecutive days; 5 cc. on the fourth day and 10 cc. either every day with the exception of Sunday or else every other day for the 2 weeks following. Subsequently, injections of the ferric salt solution (10 cc. each time) were made 3 times a week for a period of about 17 weeks. In comparison with previous experiments⁷ the period of injection was now doubled in its duration and some of the rabbits received almost 3 times as much ferric chlorid as was administered to rabbits of the preceding series.⁷ The ferric salt solution was kept on ice when not in use. It was gently heated before each intravenous injection. The latter were always given very slowly. In spite of these precautions, ferric chlorid in the concentrations used was in a few instances found toxic for rabbits. Injections in these animals was followed by immediate death. Five animals were thus lost in the course of this study. It was found, as a rule, that small initial doses of the ferric salt solution increases the tolerance of the animal, so that subsequently considerably higher amounts could usually be injected without any untoward effect.

The rabbits used were all brindle in color and of the variety known to the animal breeders as "Flemish." The total amount of ferric chlorid injected in each rabbit varied from 130 to 620 cc. of a 0.25 per cent solution. Both experimental and control animals were weighed every week during the course of the experiment. The weighing was always performed at about the same time of day. The animals were so distributed that usually from 2 to 4 rabbits were kept in a single cage.

The results are based on a study of 36 rabbits; 20 of these were allowed to die of their disease in order to compare the survival time of control and experimental animals. A postmortem examination was performed on each rabbit. Usually specimens of lung, liver, spleen, kidney and bone marrow were fixed in 10 per cent formalin and stained with hematoxylin and eosin for microscopic examination. Sections of lung tissue of several rabbits were stained for the presence of tubercle bacilli. Tests for the presence of iron in tubercles of lung tissue were also performed (Prussian blue reaction). The remaining 16 rabbits of the series were sacrificed between the forty-fifth and the seventy-ninth day after inoculation with tubercle bacilli. In this way the extent of tuberculous lesions, particularly as observed in the lungs, was compared in control and experimental animals when both had had the disease for the same length of time.

Effect of Ferric Chlorid Injections on the Survival Time of Tuberculous Rabbits. The results of the experiments are shown in Table 1. The survival time of 10 control rabbits varied from 71 to 124 days, with an average of 94 days. The survival time of 10 experimental animals ranged between 89 and 190 days, with an average of 135 days. Granting the marked individual variations, it is clear, nevertheless, that the values of the survival time in the experimental group are consistently shifted to a higher level than in the controls. The average increase in survival time of experimental rabbits over that of controls as a result of repeated intravenous injections of ferric chlorid is 41 days. It is interesting to note that in the previous series⁷ the average increase was 48 days. The results obtained in the present series are, therefore, essentially confirmatory. Larger quantities of ferric chlorid administered over a longer period of time have failed to produce more striking results in regard to prolongation of life than had previously been obtained.⁷

TABLE 1.—EFFECT OF FERRIC CHLORID INJECTIONS ON TUBERCULOUS RABBITS.

Control animals.				Experimental animals.				
Rabbit No.	Weight at beginning of experiment, gm.	Prussian blue reaction in tubercles of lungs.	Survival time after inoculation with tubercle bacilli, days.	Rabbit No.	Weight at beginning of experiment, gm.	Amount of 0.25 per cent ferric chlorid injected, cc.	Prussian blue reaction in tubercles of lungs.	Survival time after inoculation with tubercle bacilli, days.
3-00	2130	0	71	3-24	2360	240	++	89
3-66	2640	0	73	3-25	2320	250	++	90
3-29	2160	Trace	77	3-13	2280	270	++	97
3-21	2060	0	79	3-17	2710	340	++	112
3-27	2700	+ to ++	89	3-01	2780	420	++	119
3-18	2170	Trace	95	2-89	2740	420	+++	134
3-37	2800	+	102	4-13	2830	555	+	151
3-38	3115	0	105	3-15	2125	620	+++	182
3-35	2690	0	123	3-09	2315	526	++	184
4-20	2250	+	124	3-22	2920	610	++	190
Av.	94	135

Within a few minutes after dipping the lung tissue of the experimental rabbits into acidified potassium ferrocyanid an intense Prussian blue reaction appeared in the caseous centers of tubercles. The intensity of the color is indicated in Table 1 by the number of plus signs. The lung tissue of control rabbits either showed no Prussian blue reaction or, in some cases, it appeared to a relatively slight extent after the tissue had been bathed in potassium ferrocyanid for some time. In this connection it is to be noted that, as pointed out in a previous publication,⁶ the Prussian blue reaction is occasionally positive in the caseous areas of a control rabbit, particularly if some degree of postmortem change has occurred.

The average change in weight, both in control and experimental animals throughout the duration of the experiment is represented in Chart I. The average weight in both groups was practically the same at the time of inoculation with tubercle bacilli. The control and experimental rabbits increased in weight for the first 3 weeks of the disease. The period of ferric chlorid injections was started during the fourth week. The experimental animals showed a slight increase in weight during the first part of this period. This was followed by a gradual fall in weight terminating in the death of the last experimental rabbit 27 weeks after inoculation with tubercle

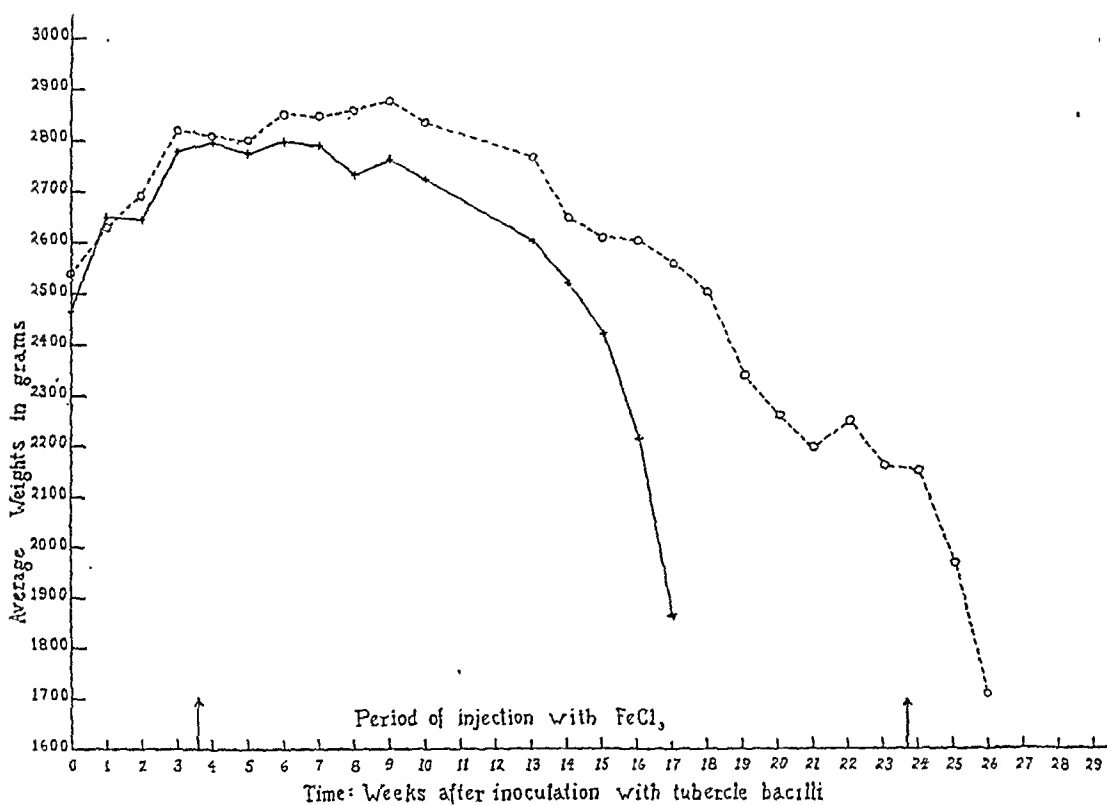


CHART I.—Average weight changes of tuberculous rabbits repeatedly injected with ferric chlorid, and of control tuberculous rabbits. —x—, control rabbits; ---o---, experimental rabbits.

bacilli. The control group showed no average increase in weight during the period when the experimental animals were receiving ferric chlorid injections. At the tenth week an abrupt fall in weight occurred, terminating in the death of the last of the control rabbits by the seventeenth week of the disease. The lag in the fall in weight of experimental rabbits, as seen in Chart I, is correlated with the increase in the survival time of this group (Table 1), and also as will be shown presently with a retardation in the development of tuberculous lesions in the lungs.

The average gain or loss in weight in both experimental and

control animals from 1 week to the next throughout the duration of the experiment is plotted on Chart II. The control group shows a progressive increase in loss in weight per week, beginning at the eleventh week and extending to the seventeenth week after inoculation with tubercle bacilli. The experimental group, on the other hand, shows a constant weekly loss in weight, though at a higher level than in the controls, during the period extending from the eleventh to the twenty-fourth week of the disease. At this time the injections of ferric chlorid were discontinued. This was followed by an abrupt fall in weight which terminated in the death of the last of the experimental animals about 3 weeks later.

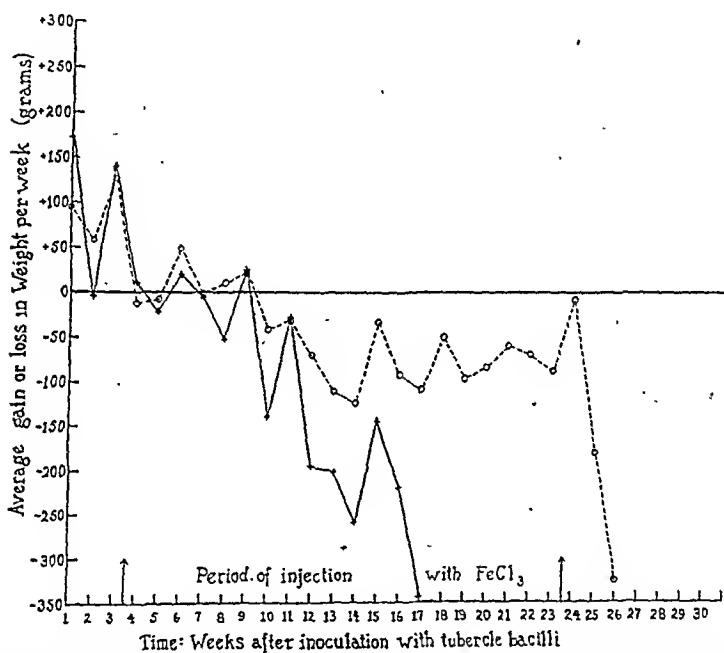


CHART II.—Average gain or loss in weight from week to week in tuberculous rabbits repeatedly injected with ferric chlorid, and in control tuberculous rabbits. —x—, control rabbits; ---o---, experimental rabbits.

Some of the organs, notably the lungs, in both the control and experimental rabbits were studied in the gross and microscopically at the time of death. A comparison of the pathologic appearance of the lungs revealed strikingly fewer tubercles in the 4 animals of the experimental series which survived for the shortest length of time (89 to 112 days, Table I) as compared with the corresponding 4 of the control group (71 to 79 days). On gross examination, the lungs of these short-lived experimental rabbits exhibited discrete caseous foci in an irregularly congested parenchyma. Microscopic study showed, in addition to discrete caseating lesions with mono-



FIG. 1.—Comparison of lung of Rabbit 3-27 (control, 89 days) and that of 3-25 (experimental, 90 days). Both of these animals were allowed to die of their disease. Rabbit 3-25 had received by repeated intravenous injections a total of 280 cc. of 0.25 per cent ferric chlorid. Both of these animals died at about the same time; note the difference in the extent of the tuberculous lesions.

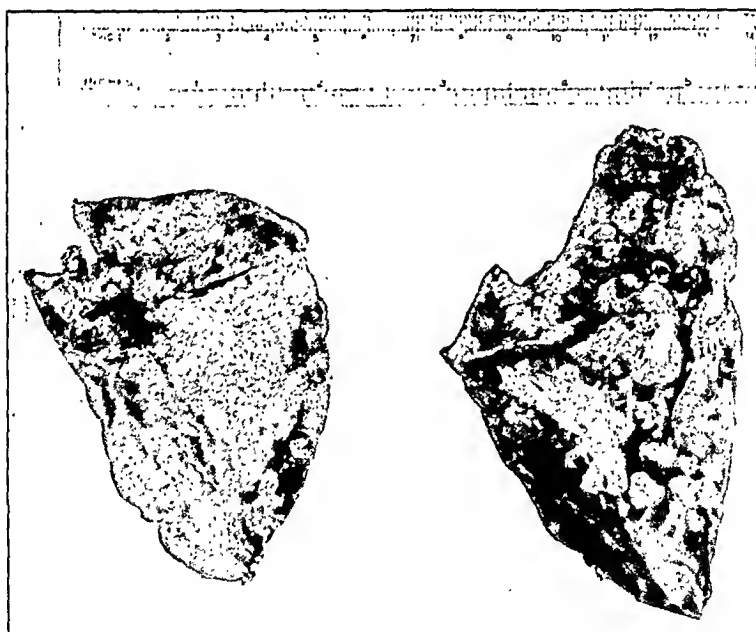


FIG. 2.—Lung of Rabbit 3-66 (control) and that of Rabbit 2-89 (experimental). Both of these animals were allowed to die of their disease. Rabbit 2-89 had received by repeated intravenous injections a total of 420 cc. of 0.25 per cent ferric chlorid. Note that the extent of tuberculous involvement found in the control lung (73 days) was approximately duplicated in the experimental group only at a considerably later period (134 days).

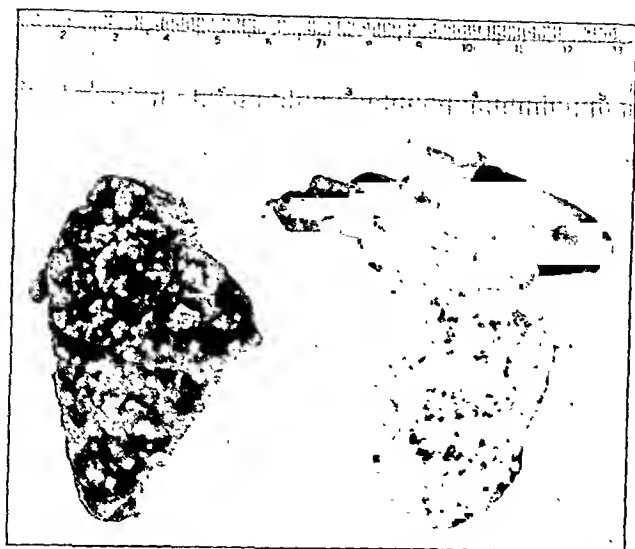


FIG. 3.—Lung of Rabbit 4-20 (control) and that of Rabbit 3-09 (experimental). Both of these animals were allowed to die of their disease. Rabbit 3-09 had received by repeated intravenous injections a total of 526 cc. of 0.25 per cent ferric chlorid. Note that the degree of tuberculous involvement in the lung taken from among the longest experimental survivors (184 days) is not greater than that found in the longest survivor of the control group (124 days).



FIG. 4.—Comparison of lung of Rabbit 3-78 (control) and that of Rabbit 3-32 (experimental). Both of these animals were killed on the fifty-sixth day of their disease. Rabbit 3-32 had received by intravenous injections a total of 151 cc. of 0.25 per cent ferric chlorid. Although both of these animals were killed on the same day, the difference in the extent of the tuberculous lesions is striking. To illustrate the type of scale used in compiling the results of Table 2 the number of + signs indicate the extent of the lesions: Rabbit 3-78, control +++; Rabbit 3-32, experimental +.

nuclear phagocytic infiltration, a considerable extravasation of red cells in several areas, alveoli plugged with serum and infiltration of polymorphonuclear leukocytes at the peripheries and centers of some tubercles. Considerable fibrin deposits were also observed. The lungs of those surviving for the shortest time in the control group were enlarged and consolidated with extensive confluent tuberculous lesions. Gelatinous exudation in alveoli and polymorphonuclear infiltration were infrequently seen in these 4 control animals. Judging by the degree of tuberculous involvement and, as described above, by the type of lesion in the lungs of experimental rabbits that had died at a relatively early date (Table 1), it is quite possible that the cause of death in these animals was in part the widespread exudative inflammatory reaction in the alveoli that one usually associates with the phenomenon of allergy. It is also to be noted that Rabbit 3-17 revealed at postmortem a massive infection in both ears, with an itch mite belonging to the *Sarcoptes* family. When the lungs of those dying first in the experimental group were compared with the lungs of control rabbits that had survived for an equal length of time, the difference both in number and extent of tuberculous lesions was striking. (Fig. 1.) The lung of the control (Rabbit 3-27, 89 days) shows numerous caseating foci with extensive confluence of lesions. The lung of the experimental (Rabbit 3-25, 90 days), on the contrary, shows fewer and discrete foci with relatively little confluence of lesions.

In comparing the degree of pathologic involvement in the control and experimental animals, it was found that the lung of a control surviving 73 days was best matched in the extent of its tuberculous lesions by the lungs of experimental rabbits that had survived 119 or 134 days. (Fig. 2.) The lungs showed massive consolidation with extensive confluence of lesions. Microscopic examination revealed in both cases a parenchyma replaced by large conglomerated caseating areas with diffuse mononuclear phagocytic infiltration at their peripheries. The control lung (Rabbit 3-66, 73 days) showed considerable invasion and plugging of the lumina of bronchioles primarily by mononuclear phagocytic cells. In the experimental (Rabbit 2-89, 134 days) a moderate proliferation of fibrous tissue was seen at the periphery of some of the tubercles. It is of interest to note that the rabbits of the experimental series surviving longest (184 to 190 days) failed to show more tuberculosis in the lungs than the last survivors in the control group (123 and 124 days). This fact is illustrated in Fig. 3.

In brief, comparison of the tuberculous involvement in the lungs of control and experimental animals seem to indicate that concomitantly with the accumulation of iron in caseous areas, there is a retardation in the progress of the lesions. These findings accord with the curves of average weight and with the increase in the survival time of the experimental rabbits (Table 1 and Chart I).

A brief summary of a few typical protocols of the postmortem examination (of the lungs in particular) is presented:

Protocols. Rabbit 3-66. Control. Survival time, 73 days; lungs enlarged, massive confluent caseating tuberculosis; lesions vary in size, averaging 10 to 12 mm.; kidneys studded with discrete caseating foci, 1 to 2 mm. in size; no gross evidence of tuberculosis in liver and spleen. Microscopic examination of lungs reveals large caseating areas in a parenchyma diffusely infiltrated with mononuclear phagocytes; lumina of bronchioles invaded in several instances largely by mononuclear cells from adjacent tubercles; few thrombosed vessels seen in lung parenchyma; liver cells show numerous hemosiderin-like granules within their cytoplasm; large amount of this same material in phagocytic cells of the spleen.

Rabbit 3-27. Control. Survival time, 89 days; lungs not enlarged; extensive confluent tuberculosis in many areas; lesions range between 1 mm. to several centimeters in size; microscopic examination shows confluent caseating lesions, many of which contain large deposits of calcium; diffuse mononuclear reaction replaces normal lung parenchyma. In some parts many of these cells and some polymorphonuclears plug the lumina of bronchioles; capillary congestion at the periphery of some of the tubercles; groups of alveoli filled with gelatinous exudate. Small foci of polymorphonuclear cells occasionally observed; metaplasia of alveolar epithelium into cuboidal type seen in several areas. No gross evidence of tuberculosis in kidney, liver and spleen.

Rabbit 3-35. Control. Survival time, 123 days; lungs small and show moderate amount of caseating tuberculosis in the right lung; confluence of lesions at base; left lung congested; discrete caseous foci throughout parenchyma. Microscopic examination shows alveoli plugged with gelatinous exudate containing many mononuclear phagocytes; lymphatics dilated with their lumina occluded by fibrinous strands; tubercles are either discrete or confluent; caseating material surrounded by epithelioid mononuclear phagocytes and lymphocytes; polymorphonuclear infiltration fairly extensive; fibrous proliferation about some of the lesions; a few alveoli plugged by extravasated red cells; numerous tubercle bacilli in caseous material. No gross evidence of tuberculosis in kidneys, liver and spleen. Considerable number of hemosiderin-like granules within liver and Kupffer cells.

Rabbit 3-13. Experimental. A total amount of 270 cc. of 0.25 per cent ferric chlorid injected; survival time, 97 days; lungs small; left lung congested; few and small discrete tubercles, averaging in size 3 to 4 mm.; no confluence of lesions; trachea occluded by viscid, yellowish suppurative material. Microscopic examination reveals large numbers of alveoli plugged with gelatinous exudation. Considerable amount of delicate fibrinous deposits in some of the alveoli and within the lumen of vessels; lesions contain many polymorphonuclear leukocytes; tubercles made up of caseous centers with collections of epithelioid cells interspersed with polymorphonuclear cells about them; engorgement of capillaries and extravasation of red cells seen in a number of areas; few discrete foci in kidneys; spleen and liver not remarkable.

Rabbit 2-89. Experimental. A total amount of 420 cc. of 0.25 per cent ferric chlorid injected; survival time, 134 days. Lungs enlarged; massive consolidation with confluent caseating tuberculosis throughout both lungs. Microscopic examination shows large confluent caseating areas in a parenchyma diffusely infiltrated with mononuclear phagocytes; moderate connective tissue proliferation at the periphery of tubercles. Kidneys studded with miliary foci; large conglomerated lesions in right kidney, about 5 mm. in size; hemosiderin-like granules in cells of glomerular tufts; similar material scattered in some of the cells lining many tubules. These granules

produced a positive Prussian blue reaction when sections were treated with acidified potassium ferrocyanid; this same hemosiderin-like material seen scattered within liver cells, Kupffer cells and mononuclear phagocytes in the bone marrow.

Rabbit 3-22. Experimental. A total amount of 610 cc. of 0.25 per cent ferric chlorid injected. Survival time, 190 days; lungs studded with discrete caseous foci, ranging in size from 1 to about 8 mm., the majority being 2 or 3 mm.; relatively little confluence of lesions. Microscopic examination shows conglomerated tubercles with large proliferation of mononuclear phagocytes at the peripheries; a moderate amount of fibrous tissue proliferation; large calcium deposits within some caseating areas; clumps of tubercle bacilli scattered within the peripheral portion of caseous material. Kidneys show rare discrete foci. No gross evidence of tuberculosis in liver and spleen.

Effect of Ferric Chlorid Injections on the Extent of Tuberculous Lesions in the Lungs. As pointed out at the beginning of this paper, an additional 16 rabbits were inoculated intravenously on the same day and with the same suspension of bovine tubercle bacilli as the animals in the series discussed above. These rabbits were killed at various intervals of time. This was done in order to compare the progress of the disease, as indicated by the extent of the pulmonary lesions, in the control and experimental animals. In addition, 8 rabbits taken from the preceding group of control and experimental animals, all of which had died early of their disease, were studied in regard to the extent of the lesions. Thus 24 animals in all were used, 12 of which had had repeated intravenous injections of 0.25 per cent ferric chlorid beginning on the twenty-seventh day after inoculation with tubercle bacilli. The interval between the injection of tubercle bacilli and the death of the animals ranged between 45 and 97 days. The lungs of an experimental animal were compared with those of a control that had had the disease for approximately the same interval of time.

TABLE 2.—EFFECT OF FERRIC CHLORID INJECTIONS ON THE EXTENT OF TUBERCULOUS LESIONS IN LUNGS.

Control animals.				Experimental animals.				
Rabbit No.	Weight at beginning of experiment, gm.	Interval between injection of tubercle bacilli and death of animal, days.	Extent of tuberculous involvement.	Rabbit No.	Weight at beginning of experiment, gm.	Interval between injection of tubercle bacilli and death of animal, days.	Amount of 0.25 per cent ferric chlorid injected, cc.	Extent of tuberculous involvement.
3-36	2660	46	+	3-11	2520	45	130	Trace
3-78	2560	56	+++	3-32	2405	56	151	+
3-10	2535	59	++	3-16	2515	59	172	+
1-17	2040	60	++	3-33	2175	61	180	+
3-66*	2640	73	+++	3-30	2665	73	240	++
3-29*	2160	77	+++	2-95	2195	76	200	++
3-34	2720	78	++	3-23	2780	78	197	+
3-14	2510	78	+	3-03	2310	78	210	+
3-88	2195	79	++	3-05	2420	79	176	++
3-21*	2060	79	+++					
3-27*	2700	89	++	3-24*	2360	89	240	+
				3-25*	2320	90	280	+
3-18*	2170	95	++	3-13*	2280	97	270	+

Trace = small, discrete caseating lesions averaging about 2 to 3 mm. in diameter. + = discrete, caseating lesions averaging about 5 mm. in diameter; no confluence of lesions. ++ = numerous caseating foci with some confluence of lesions. +++ = lungs enlarged, massive caseating tuberculosis with extensive confluence of lesions.

* These rabbits were allowed to die of their disease; all others were killed.

The results of this study are summarized in Table 2. An explanation of the comparative scale used accompanies the table. It is clear that in all cases with the exception of 2 rabbits (*i. e.*, in 83 per cent of the animals) the tuberculous lesions in the lungs were less extensive in the experimental than in the control group. Fig. 4 illustrates the type of results obtained. The observations indicate that repeated intravenous injections of ferric chlorid retard the development of tuberculous lesions in the lungs of rabbits inoculated with a bovine strain of tubercle bacilli.

Microscopic examination of lungs of control and experimental rabbits substantiated essentially the results found in the gross. A brief summary of a few protocols is presented.

Protocols. *Rabbit 3-36. Control.* Killed 46 days after inoculation with tubercle bacilli; large areas of conglomerated caseating foci with diffuse mononuclear phagocytic infiltration at periphery; no gelatinous exudation within alveoli.

Rabbit 3-11. Experimental. Killed 45 days after inoculation with tubercle bacilli; a total of 130 cc. of 0.25 per cent ferric chlorid administered; small discrete foci of mononuclear cells with little caseation; no gelatinous exudation within alveoli.

Rabbit 3-78. Control. Killed on fifty-sixth day of the disease; very extensive confluence of caseating lesions with diffuse mononuclear infiltration at the peripheries; large numbers of bacilli in caseous material.

Rabbit 3-32. Experimental. Killed on fifty-sixth day of the disease; a total of 151 cc. of 0.25 per cent ferric chlorid administered; lungs show discrete foci of mononuclear cells with practically no caseation and an absence of confluence.

Rabbit 3-10. Control. Killed on fifty-ninth day of the disease; lungs show very extensive caseating lesions which are confluent; large calcium deposits in caseous areas; moderate fibroblastic proliferation about the lesions; extensive areas infiltrated with mononuclear phagocytes; no tubercle bacilli found.

Rabbit 3-16. Experimental. Killed on fifty-ninth day of the disease; 172 cc. of 0.25 per cent ferric chlorid administered; lungs show many large foci of caseation with diffuse infiltration of mononuclears at their periphery; small amount of confluence and no calcium deposits; few acid-fast organisms found in the lesions.

The observations reported in this communication indicate that concomitantly with an accumulation of iron from the circulating blood into caseous areas of tubercles, the course of the disease in the rabbit is protracted as evidenced both by a retardation in the development of the tuberculous lesion and by a definite increase in the survival time of the injected rabbits. The increase in the survival time confirms the findings obtained in a previous series of animals.⁷ It remains to be seen whether the effects obtained are entirely due to the accumulation of iron in tuberculous foci; for it is conceivable that there may be other factors involved in producing the results. Whether repeated intravenous injections of ferric chlorid will produce similar effects on animals other than the rabbit and infected with different types of tubercle bacilli, remains also to be seen.

Further studies are being conducted to investigate these questions.

Conclusions. Repeated intravenous injections of ferric chlorid are followed by an accumulation of iron in caseous areas of tubercles and by a definite increase in the survival time of tuberculous rabbits.

Studies of weight changes and comparison of the pathologic involvement in the lungs of the control and experimental animals at various intervals indicate that the intravenous administration of ferric chlorid protracts the course of the disease.

Repeated intravenous injections of ferric chlorid retard the development of tuberculous lesions. This is indicated by comparing the extent of the pulmonary lesions in control and experimental animals having had the disease for the same length of time.

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TIME AND DOSAGE AS FACTORS IN THE CURE OF SYPHILIS.

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ALTHOUGH routine antisyphilitic treatment may vary somewhat in different clinics, a fundamental uniformity in schedules emphasizes the general acceptance of certain factors governing the successful administration of antisyphilitic remedies. The physician is armed with potent specific drugs but he recognizes that the cure of the patient will result from the interaction of a number of forces. The tissue defense mechanism will contribute substantially to the therapeutic result and a lapse of time during which this defense action may evolve is one necessary factor in the cure of the disease.

Thus it has come to be recognized that a "therapeia magna sterilisans" of Ehrlich rarely exists in practice and that direct spirocheticidal action is not solely responsible for the effect obtained. It is, therefore, of prime importance for the physician treating

patients suffering from syphilis to keep clearly in mind the relationships which undoubtedly exist between dosage, lapse of time and therapeutic effect. He should also be in a position to appreciate and evaluate the disadvantage of any great deviation from optimum schedules of treatment. Clearer conceptions of the interplay of various factors are always obtained if the information available can be reduced to graphic form; in other words, if it can be plotted. Such is the purpose of this paper.

In 1919¹ and 1921² the author published data on therapeutic results obtained from the administration of arsphenamin in the

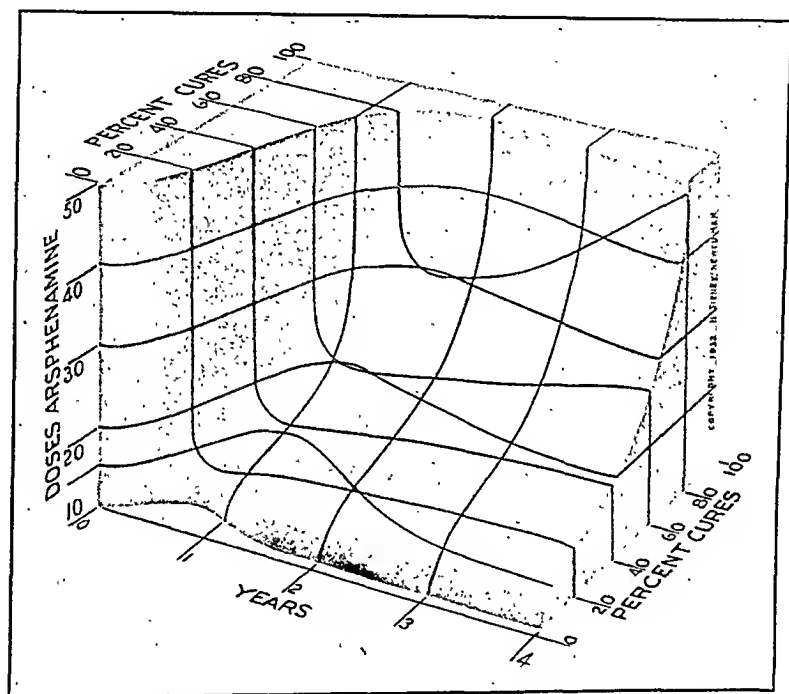


Fig. 1.—Therapeutic surface. Seropositive, primary and secondary syphilis.

treatment of syphilis. Further data resulting from new clinical material together with later information about the cases which had already been studied were subsequently collected but not published. In 1926 Moore and Keidel³ published several papers on the treatment of syphilis presenting similar data in a different form, while from time to time other publications have appeared which contribute to this general data.

In this paper we tabulate results obtained at the Pennsylvania Hospital, and from this and from other available information we develop a graphic portrayal of the therapeutic effect to be expected from arsphenamin in the treatment of syphilis. Since this graphic

representation involves three factors it must be drawn in three dimensions and it results in a surface. Such surfaces are portrayed in Figs. 1 and 2.

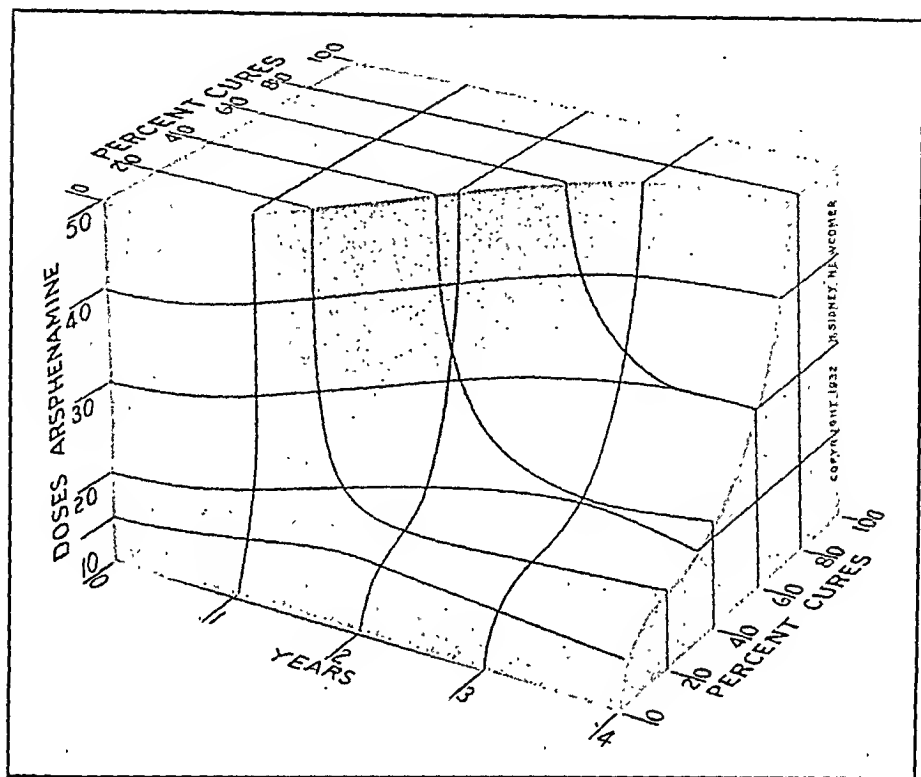


FIG. 2.—Therapeutic surface. Late syphilis.

Surfaces in three dimensions, being the locus of "cured" patients treated with varying amounts of arsphenamin during varying periods of time. The vertical axis represents doses of arsphenamin, starting with 10 doses for the base line. The horizontal axis represents time in years. Depth represents cures in per cent for an average large group of individuals. The intersections with the surface of planes passing through the enumerated subdivisions along the coördinate axes give curved lines which serve as reference lines for the location of data points on the surface.

Table 1 gives data for patients having seropositive, primary and secondary syphilis. Table 2 gives similar data for patients having tertiary syphilis. The lesions in tertiary syphilis are much too varied to allow of any simple or certain classification into subgroups. Most of the patients with late syphilis came to the syphilis clinic from the dispensary of a general hospital and are typical of the various manifestations found at this stage of the disease. Very few of the patients tabulated had neurosyphilis, about 3 per cent were tabetic and there were no cases of general paresis.

The technique employed for the Wassermann reaction of the individuals tabulated included the use of both an acetone insoluble and a cholesterinized alcoholic extract antigen. For patients who have received treatment the latter antigen is the most reliable, but it will sometimes give a positive reaction in the case of patients not having syphilis. The proper interpretation of the Wassermann reaction requires considerable experience and it is impossible to put in writing the criteria on which judgments are to be based. The author has previously published observations on the Wassermann

reaction⁴ and given examples of confusing cases.¹ Such examples could be multiplied many times but no charts can replace a study of the patients themselves.

TABLE 1.—SEROPOSITIVE, PRIMARY AND SECONDARY PATIENTS.

	6 to 12 mos., over 10 doses.	12 to 18 mos., under 25 doses.	Silver arsphena- min.	18 mos. or over.	Over 30 mos.	H.S.N., 1918 cases.	H.S.N., 1920 cases.	Over 25 mos., over 35 doses.
Average time, mos.	9	12.5	15.5	21.4	46.4	8	18	43
Average doses	15.4	14.7	23.5	18	17.6	21	27	44.8
Per cent negative	28.5	28.5	50	61	73	46	55	33
Per cent doubtful	28.5	21.5	30	6	0	0	0	5
Probable cures, per cent	12*	20*	60	60	73†	35	75	35/85
Number of patients	14	14	20	18	11	13	13	12

TABLE 2.—SEROPOSITIVE TERTIARY PATIENTS.

	6 to 12 mos., over 10 doses.	12 to 18 mos., under 25 doses.	Silver arsphena- min.	18 mos. or over.	Over 30 mos.	H.S.N., 1918 cases.	H.S.N., 1920 cases.	Over 36 mos., over 25 doses.
Average time, mos.	9.3	13.6	19	21.4	42.1	11	27	50
Average doses	16.4	16.2	26.5	20.5	20.6	22	38	45.2
Per cent negative	0	4	10	10.5	43	0	47	29
Per cent doubtful	16	10	20	27	10	0	18	21
Probable cures, per cent	0	3	20	22	45	0	50	35/70
Number of patients	43	50	80	48	30	17	17	24

The patients represented in the tables are divided into groups of individuals who have had very roughly equal amounts of treatment over equal intervals of time. The figures in the columns give for each group the average number of months under treatment, the average number of doses received, the per cent of individuals who have become apparently permanently negative, the per cent who are negative without any evidence that they are permanently so, and an estimate as to how many of both classes of patients will continue negative. The last line gives the number of patients in each group.

Except for Columns 6 and 7, no patients are represented twice. The columns headed H.S.N. tabulate previously published data. The last column tabulates patients who were particularly stubborn in yielding to treatment and, therefore, includes an undue proportion of incurables. For these patients 2 figures are given for probable cures: 1 for the group and 1 for a hypothetical representative group.

Although little is definitely known as to the significance of a continuously negative Wassermann reaction, it is probable that repeatedly negative reactions indicate improvement when they are obtained in patients previously positive and clinically well under treatment. When the reactions are continuously negative over a period exceeding 1 year it may be assumed that a permanent change in the patient's condition has taken place and that the Wassermann reaction will continue to be negative. Although there are exceptions to this statement, for statistical purposes it is useful to speak of such patients as "cured."

In the accompanying tables "doubtful" indicates patients who appear clinically cured and have a Wassermann record showing definite improve-

* These estimates are obviously too small to fit the surface (Fig. 1); 25 and 30 would be more appropriate numbers and are not inconsistent with the data of the third and fourth lines.

† This number is too large to fit the surface but is less out of line when consideration is taken of the fact that the long period of time refers to an observation period rather than a treatment period.

ment toward the negative but not negative for a sufficiently long period of time to be termed "cured."

Individuals tabulated in the first two groups were under observation only a short time. It is not possible to classify any of these as permanently negative but an estimate is made based on the negative Wassermann record and the clinical picture for that time.

The patients in the third column received silver arsphenamin. In the second and third columns from the last of both tables data from previously published cases is used.^{1,2} In some instances these patients have been followed for a longer period of time and their subsequent history has then been consistent with the data first published.

In the last column of each table are placed the cases particularly stubborn in yielding to treatment. They differ from all the other groups in the large amount of arsphenamin administered and the time under treatment. Such a group tends to include more than its just proportion of incurables as more fortunate patients leave the clinic as they improve. For this column, therefore, two figures are given for the number of probable cures, one for the actual group and one for a hypothetical representative group, the latter figure being used in the graphic analysis.

It is possible by reference to the treatment data originally published in detail² to extend the amount of statistical information to time intervals and dosages other than those set forth in the tables.

In the majority of cases the tertiary patient who is likely to be cured becomes negative during 3 years of treatment. At the end of the first year about 3 per cent of the patients tabulated appeared to be negative; while at the end of the second year, depending on the amount of treatment received, the number of cures ranged from 25 to 40 per cent. The group of patients (Column 4, Table 2) who were only 22 per cent negative received insufficient treatment. There is no representation in this table of a group who had received the ideal treatment of 30 doses in 2 years but by interpolation from the table it is very probable that about 40 per cent of such patients would be negative at the end of 2 years, while at the end of the third year cures should increase to approximately 60 per cent. As a matter of fact those patients listed in the next to the last column of Table 2 showed approximately 40 per cent of cures at the end of 24 months.

The data of Table 1 for seropositive, primary and secondary syphilis are subject to somewhat the same analysis. The figures in the fifth line for probable cures were made before the concepts set forth in this article were developed and the first 2 figures, 12 and 20 of this line, are obviously underestimates.

As additional data used in developing the surface of Fig. 1 we have not only the general information which may be deduced from generally used therapeutic schedules, but we have specific information given in the article by Moore and Keidel.³

Moore and Keidel, in their article, state: "Only 10 per cent of patients receiving 8 or less doses of arsphenamin without mercury were cured. When two courses of arsphenamin plus mercury were given 37 per cent were cured, after three courses 56 per cent and after four or more courses 79 per cent of probable cures were obtained. With the utmost coöperation

on the part of the patient, and painstaking treatment and follow-up on the part of the physician, it appears possible to cure 100 per cent of patients with seronegative primary syphilis, but only 80 to 95 per cent of those with seropositive primary or secondary syphilis. The refractory 5 to 20 per cent seem likely in spite of the utmost efforts of therapy to develop late syphilis, especially neurosyphilis."

There is no essential discrepancy between this information and that obtained at the Pennsylvania Hospital. Moore and Keidel's routine treatment, which consists in administering arsphenamin in courses of 6 doses interrupted by rest intervals of 4, 6, 8 or 10 weeks, fixes within certain practical limits the number of doses which the patient may receive in any given period of time and, therefore, determines the time interval which must elapse before the cures spoken of by these authors could be effected. The data of Moore and Keidel are, therefore, subject to tabulation in a form similar to that of Table 1.

In this paper it is assumed that the patient has the benefit of mercury or bismuth in addition to arsphenamin therapy. We are also justified in assuming that the arsphenamin was of good quality and given in optimum doses.

A consideration of arsphenamin as the chief therapeutic agent involves taking account of the number of doses given, the time interval of treatment and the result in percentage cures. Plotting therapeutic effect as a function of time and number of doses results in a surface in a three dimensional space.

In the following discussion it will be seen that the actual quantitative figures become relatively unimportant in relation to the character of the surface which they determine and that the interpretation of the form of the surface gives information of much greater value than any consideration regarding the exact accuracy of the data from which it is obtained, the form of the surface being, in fact, remarkably independent of the accuracy of the data.

Seropositive Primary and Secondary Syphilis. Almost universally it is considered good practice to give such individuals "intensive arsphenamin treatment," *i. e.*, at least 1 dose a week with relatively short rest intervals between courses, the rest intervals increasing in length from time to time.* If the known data be plotted it becomes apparent in the first place that a small number of doses, for instance, 10, cannot give as a maximum much more than 10 per cent of cures. These doses would have been given in the first 3 months. Experience indicates that there will be some delay in the Wassermann reaction becoming negative, that is, the effectiveness of this treatment becomes apparent only after the lapse of a certain period of time.

If the doses are spread too thinly over the first year the number of cures will fall off and as the time over which the doses are distributed is increased a less and less number of patients will be

* For a scheme of treatment, see H. N. Cole.¹

cured; finally no cures can be added by inadequate subsequent treatment of those who failed to become negative following the first 2 or 3 doses.

If we increase the number of doses available to 15, the time interval lengthens somewhat and the therapeutic effect is greatly increased, the maximum being about 35 per cent.

It is pretty well established that this optimum of 35 per cent of cures can be obtained only when the arsphenamin is given according to the well-established regimen of weekly doses, interspersed by proper rest intervals during which mercury or bismuth is administered. Practical time considerations fix the maximum effect obtainable somewhere toward the end of the first year. It is obvious that as the doses are spread more and more thinly over the first and subsequent years the number of cures effected will drop off.

Thus the "therapeutic surface" shows a hollow or valley extending through the latter part of the first year and the whole of the second year. Beyond this time a decreasing therapeutic effect is obtained with any given number of doses. Prior to this time, concentrating the doses into a shorter time interval gives less beneficial results. Complete sterilization by direct spirocheticidal action is only obtainable early and in relatively few individuals. Too massive treatment defeats its own purpose, and deprives the individual of natural tissue defense in the later stages.

Such reasoning fixes the forms of the curves for 20, 30, 40 and 50 doses of arsphenamin. If the percentages were different the form of each curve would nevertheless be the same. As the doses are increased the maximum therapeutic effect gradually shifts in time to be attained after about 2 years' treatment with 50 doses. The surface must obviously be continuous and regular and this applies not only in the direction of increasing time but also in the direction of increasing doses.

Let us consider sections of the surface made by planes corresponding to the first, second, third and fourth years. They give the vertically directed curves of Fig. 1. The form of these curves at the top and bottom, as seen when looked at from the end of the block, is fixed by considerations outside of any data. For instance, in the case of the 1-year curve the slope must be approximately vertical from 40 doses onward and must, indeed, turn on itself eventually as the number of doses is indefinitely increased. Under such circumstances toxic symptoms would eventually out-balance any therapeutic effect. Thus each of the curves as it approaches the 50-dose line and is extended to the 60-dose line must have a very steep slope, for additional therapeutic effect is not obtainable. Similar considerations hold for the interval between the first and tenth doses.

In fact a study of the possible degrees of freedom of the surface reveals that if all factors operating are taken into consideration its

form, *i. e.*, its shape, cannot be much different from that depicted in Fig. 1.

Treatment of Late Syphilis. The treatment of late syphilis presents a different situation. The sterilizing or spirocheticidal action of arsphenamin in such cases is less effective and massive treatment is no longer desirable. The defense mechanism of the patient and the resolution of the lesions plays a more important part and lapse of time must be allowed for such reaction to develop and become effective.

The situation in early syphilis after the first failure to produce complete sterilization is admirably stated by Brown and Pearce:⁵ "During the early stages of acquired syphilis our efforts may be concentrated on the destruction of the parasites, but once a characteristic lesion has been developed it is useless to attempt to prevent a systemic distribution of organisms; every part of the body is potentially infected, but it is still possible to prevent the localization and growth of spirochetes in inaccessible foci and to prevent the development of lesions which afford more or less protection against the action of spirocheticidal agents. Fortunately, Nature aids us in this in a most effective way through the adaptation of different tissues to the growth of spirochetes. Thus, the first focal infections occur in tissues that offer no great hindrance to drug action, and with the exception of the chancre, the early lesions are readily permeated by therapeutic agents."

Speaking of the more advanced stages of syphilitic infection, Brown and Pearce call attention to the increased complexity of the problem. The organisms have become established in inaccessible locations, such as the cardiovascular and central nervous systems: "It is obvious that if vigorous treatment with parasitocidal agents is begun in the early stages of syphilis and continued systematically without accomplishing the desired result, there is little hope that persistence in the use of the same methods may prove successful when the obstacles to success have been greatly increased."

The data collected at the Pennsylvania Hospital quite clearly indicate the importance of time as a factor in treatment. Here again we have to take account of a maximum obtainable therapeutic effect (of about 75 per cent) reached with approximately 50 doses of arsphenamin at the end of a 4-year interval. Additional treatment in that interval will not raise this percentage. If the 50 doses are all given during a 2-year interval the cures are decreased to about one-half the maximum obtainable.

The surface shown in Fig. 2 represents what may be expected from various numbers of doses given in different time intervals. Fifteen doses produce much less effect than in cases of primary and secondary syphilis. They may be spread over a much longer interval and still evoke the maximum effect. When the number of doses is increased to 20 the cures jump to around 35 per cent provided the doses are spread over a sufficient period of time.

The vertical curves of Fig. 2 indicate the therapeutic effect obtainable with different numbers of doses administered over periods of 1, 2, 3 and 4 years. The same considerations hold, although to a

different degree, for these patients as for the patients with early syphilis. There is a marked difference between the two sets of curves due to the fact that tertiary syphilis is not amenable to treatment in a short period of time. No matter how much arsphenamin is given in the first year, our statistical data indicate, and many clinicians have long since reached the conclusion, that much less benefit will be obtained than from treatment continued during the second and third years. This is understandable in view of the nature of the curative process as described by Brown and Pearce,⁶ and is given expression in schedules of treatment by Stokes,⁷ Moore,⁸ Harrison⁹ and others.

Returning to Fig. 1 for early syphilis, we see that the patients who were not cured by the early treatment become in fact cases of tertiary syphilis. The curative effect in the third and fourth years, particularly in the fourth year, is thus limited to figures corresponding to those found to hold in the treatment of late syphilis and shown by the surface of Fig. 2, third and fourth years. This consideration coupled with the mathematical necessity of making the surface regular determines in Fig. 1 the shape of the surface in the third and fourth years.

It is impossible in a short descriptive explanation to discuss all of the factors which necessarily operate to fix the form of these therapeutic surfaces but enough has been said to indicate that their general character is fixed within sufficiently narrow limits so that the surfaces as drawn must present the essential facts.

Summary. The "therapeutic surfaces" of Figs. 1 and 2 enable one to visualize in a striking fashion many aspects of the relationships between time and doses and expected cures of cases of syphilis. It would seem that *the proper treatment of primary and secondary syphilis involves the administration of 30 to 50 doses of arsphenamin in appropriately spaced courses over a period of 1½ to 2 years. Increasing the total number of doses above 50 is of no benefit while more than 30 given in the first year produce no additional cures.*

In the treatment of tertiary syphilis if 50 doses of arsphenamin are available, the best results will be obtained if these be given over a 4-year period rather than over a 2-year period. Such a schedule may perhaps be facilitated by spacing the injections in each course 2 weeks rather than 1 week apart. A considerable dosage of arsphenamin concentrated into the first year or two of treatment is of no benefit to the patient and is both discouraging and economically disadvantageous.

These facts and the ready visualization of expected therapeutic result afforded by the surfaces enable the physician to lay out the most rational plan of treatment with a clear appreciation of just what may be expected when for one reason or another it is not possible to follow a dosage schedule which should give optimum results.

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MACROSCOPIC EXAMINATION OF THE BLOOD.

DISCUSSION OF ITS VALUE AND DESCRIPTION OF THE USE OF A SINGLE INSTRUMENT FOR THE DETERMINATION OF SEDIMENTATION RATE, VOLUME OF PACKED RED CELLS, LEUKOCYTES AND PLATELETS, AND OF ICTERUS INDEX.

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FROM the days of Hippocrates and of Galen until the advent of microscopy, physicians were greatly concerned with the gross appearance of the blood. The ancient theory of pathology, the doctrine of the four humors was, indeed, founded on the observation that blood drawn from an unhealthy individual differs conspicuously from normal blood after clotting. As Fahraeus¹ has pointed out, the four humors correspond to the four layers which can be seen when a fairly large quantity of blood is drawn from a patient and allowed to clot, namely, (1) a lowermost dark portion (melancholia) composed of red corpuscles deprived of oxygen; (2) a bright red layer (sanguis) above this and formed by aerated red cells; (3) a grayish-white layer (mucus, phlegma) comprised of leukocytes and platelets; and (4) a yellow fluid, the blood serum (cholora). The phlegma, which was found so conspicuous in disease, not only attracted the attention of the Greeks, but of physicians for many centuries after the humoral theory had been discarded. Under such names as "crusta inflammatoria," "size" and "buffy coat," this gray layer was an index of disease even to Sydenham and to Bright. Venesection was performed in an attempt to rid the body of this noxious material.

As microscopic studies gained impetus, the macroscopic examina-

tion of the blood lost its vogue and, with the exception of hematocrit studies by Hedin,² Daland,³ Herz,⁴ Capps,⁵ and a few others,⁶ this method of blood examination was completely neglected. In 1918 Fahraeus¹ made his first observations on the suspension stability of the blood. His studies have aroused considerable interest. Working from another angle and chiefly stimulated by a paper by Haden.⁷

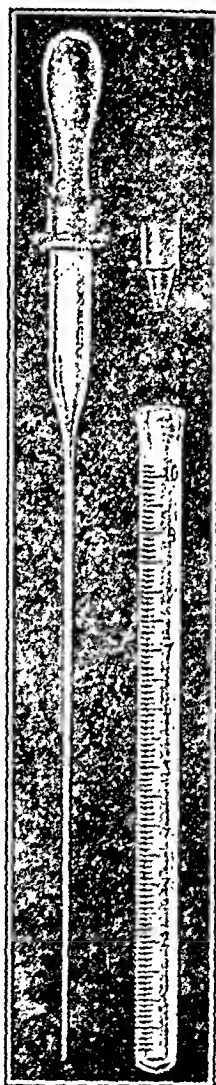


FIG. 1.—Hematocrit, pipette and bulb used for filling it, and cap for hematocrit. Two-thirds actual size. (Courtesy W. E. Prior Company, Inc.)

several students of the blood have again become interested in the determination of the volume of packed red cells by means of various types of hematocrit.⁸ The macroscopic study of the blood as a whole has not, however, regained the position of importance it held for so many centuries.

The use of a hematocrit, previously described,⁹ has in such a simple manner afforded so clear a macroscopic picture of the blood by its

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employment not only for the measurement of volume of packed red cells but also for the determination of sedimentation rate, volume of packed white cells and platelets, and of icterus index, that the following description and discussion of these uses is presented.

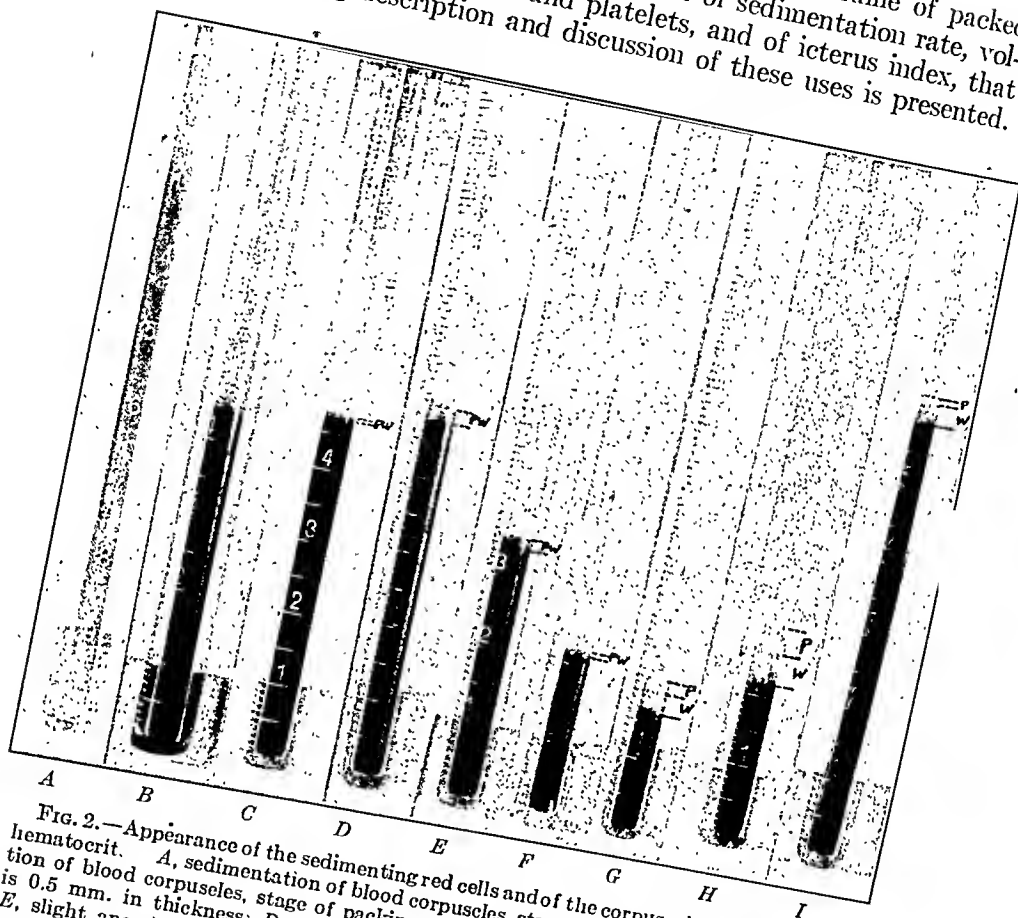


Fig. 2.—Appearance of the sedimenting red cells and of the corpuscular layers in the hematocrit. *A*, sedimentation of blood corpuscles, stage of rapid fall; *B*, sedimentation of blood corpuscles, stage of packing; *C*, normal blood; the reddish-gray layer is 0.5 mm. in thickness; *D*, no anemia; marked leukocytosis (W. B. C. 26,000); *E*, slight anemia; there is also slight leukocytosis; *F*, marked anemia; leukocyte count normal; *G*, case of myeloid leukemia, showing marked anemia; leukocytosis and thrombocytosis (R. B. C., 2.3 million; W. B. C., 35,000; platelets, 325,000); *H*, case of myeloid leukemia, showing less marked anemia (R. B. C., 3.6 million; W. B. C., 45,600; platelets, 430,000); *I*, case of polycythemia vera with leukocytosis and slight thrombocytosis (R. B. C., 6.7 million; W. B. C., 24,400; platelets, 430,000). *P* = platelet (cream-colored) layer; *W* = leukocyte (reddish-gray) layer; *PW* = layer of platelets and leukocytes (corpuscles not separately distinguished). Hematocrits *C* to *I*, inclusive, were centrifugalized until no further packing occurred.

The hematocrit (Fig. 1)* is a narrow glass tube, somewhat less than 11 cm. long, with uniform bore (about 2.5 mm.) and flat inside bottom, on which a centimeter-millimeter scale 10 cm. in length is etched. Along the right side of the scale the numbers, 1, 2 . . . 10 are marked, commencing at the first centimeter mark above the bottom. At the left side of the scale

* The instrument may be obtained from Arthur H. Thomas Company, Philadelphia.

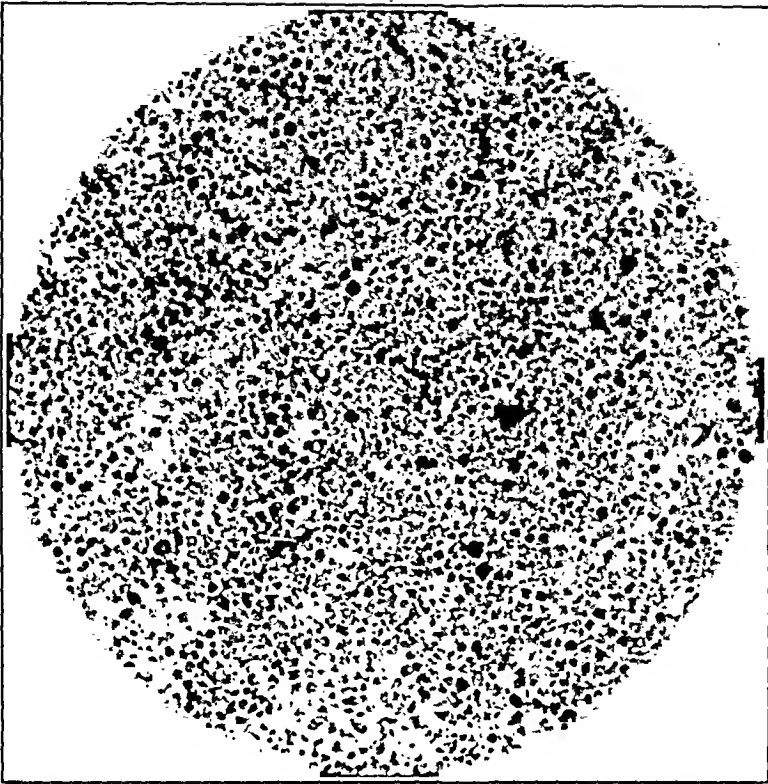


FIG. 3.—Microscopic view of the topmost, cream-colored layer of Fig. 2, *G*. Consists almost entirely of platelets. ($\times 500$.)

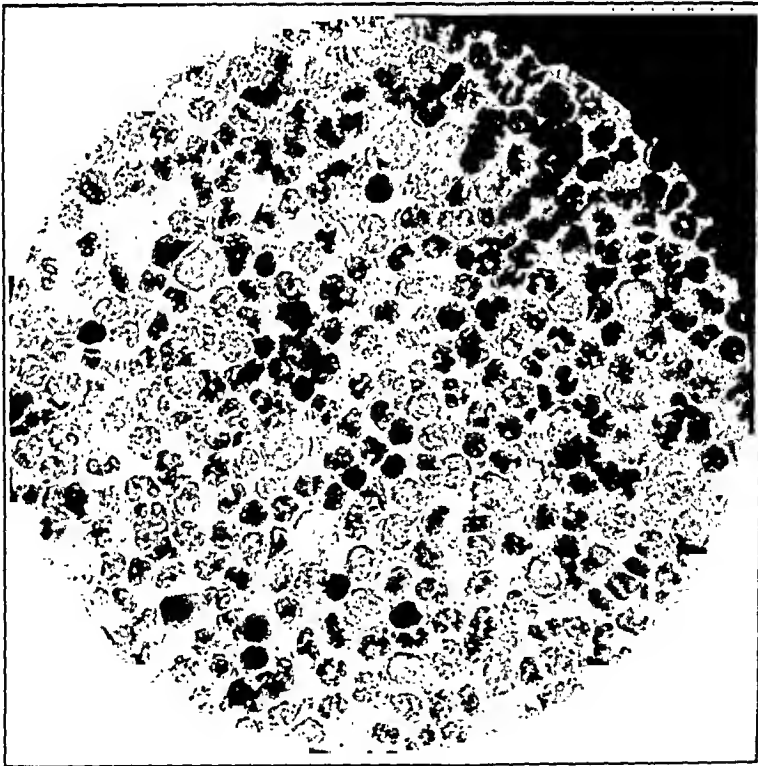


FIG. 4.—The reddish-gray layer below the cream-colored layer of Fig. 2, *G* (chronic myeloid leukemia). It is composed almost entirely of leukocytes. ($\times 500$.)

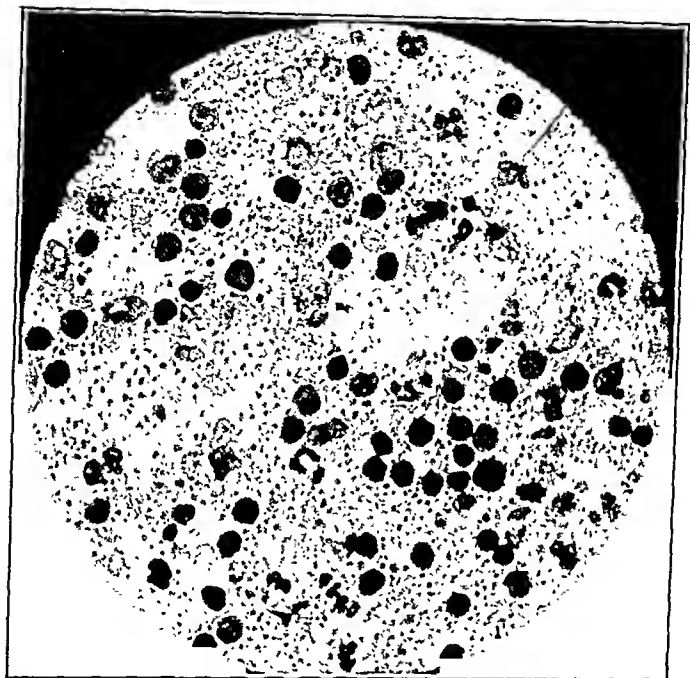


FIG. 5.—Microscopic view ($\times 500$) of material from the reddish-gray layer which was 1.1 mm. in thickness (leukocyte count, 10,050) of an infant's blood. There are many leukocytes, chiefly lymphocytes, and many platelets with scarcely any red corpuscles whatever.

the numbers 0, 1, 2 . . . 9 are found, these commencing at the upper portion of the hematocrit opposite the 10 mark. The figures at the right serve for volume readings, whereas those at the left are used for sedimentation readings.

Venous blood is obtained, care being taken to avoid congestion of the arm such as may be produced by prolonged application of the tourniquet. A clean, dry syringe and needle must be employed for drawing the blood. As anticoagulant dry potassium oxalate, 10 mg. per 5 cc. of blood, is used. In these quantities oxalate does not influence red cell, leukocyte, platelet or reticulocyte counts or the hemoglobin value, but a shrinkage in the volume of the red cells of 8.15 per cent takes place, which may be corrected by multiplying the volume of packed red cells, as read, by the factor 1.09. Our studies have shown that sedimentation-rate is not delayed by the use of this quantity of oxalate.

The chief objection which may be raised against the use of this hematocrit is that venepuncture is necessary. This is now so commonly done even for less important purposes that this disadvantage deserves little consideration. It is our general practice to collect 5 cc. of venous blood and a few blood smears (taken from the finger in the usual manner). Only 0.7 cc. of blood is required to fill the hematocrit, but by collecting 5 cc. a sufficient quantity is obtained at one time for any examinations desired and for repetition of counts which require checking. No quantitative alteration in any of the corpuscular elements occurs for at least 6 hours and usually for as long as 20 hours after withdrawal of the blood. It is important to employ a minimal and known amount of anticoagulant. Ten milligrams of potassium oxalate are most easily measured by running from a burette 0.5 cc. of a 2 per cent solution of potassium oxalate into a small bottle and allowing this to dry.

The hematocrit is easily filled by means of a capillary pipette, the narrow portion of which is of such a length that it can be passed to the bottom of the instrument. After the blood has been thoroughly mixed by inverting several times the corked vial or bottle* containing it, blood is drawn by means of a bulb into the pipette, and then, the pipette having been passed to the bottom of the hematocrit, the blood is gradually expelled as the pipette is withdrawn. This should be done so that no bubbles of air are formed in the hematocrit. The pipettes may be purchased but are easily made at a nominal cost. In order to prevent evaporation of plasma during centrifugation, the hematocrit is stoppered by means of a special cork. No special centrifuge attachment is required, the ordinary 15 mm. centrifuge metal holder being quite satisfactory. The hematocrit is easily cleaned by means of capillary pipettes similar to those employed for filling it. A very convenient arrangement is a syphon system consisting of three bottles containing water, alcohol and ether, respectively, to each of which a capillary pipette is connected. A continuous stream of water may thus be forced into the bottom of the hematocrit. After the instrument has been thoroughly cleaned it may be dried by passing alcohol and ether through it in a similar manner.

Determination of Sedimentation Rate. The test introduced to modern medicine by Fahraeus¹ is gaining increasing attention and appreciation as a nonspecific index of the presence and intensity of disease. The suspension stability (sedimentation rate) of the red blood corpuscles has been compared to fever and leukocytosis and

* We employ discarded liver-extract bottles of about 6 cc. capacity.

has been found to be more sensitive than either of these commonly used tests.¹⁰ The sedimentation test is now employed in many clinics, particularly in the tuberculosis dispensary¹¹ and in gynecologic work.¹² Some observers think that it is of general value in detecting the presence of occult diseases of infectious and toxic origin.¹³

A variety of instruments has been employed for the determination of sedimentation rate. The presentation of another instrument therefore requires some justification because the multiplicity of techniques has already led to confusion. A disadvantage of the instruments commonly employed is that they can be used only for the determination of sedimentation rate. The employment of the hematocrit for this purpose is of special value because it has been demonstrated by several observers¹⁴ that anemia magnifies and polycythemia minimizes the actual rate of sedimentation of the blood. If sedimentation is measured in a hematocrit, the volume of packed red cells may subsequently be determined without further trouble. In this way an accurate measure of the degree of anemia or polycythemia is obtained and an appropriate correction can be made. A correction chart which is applicable to the instrument here described is supplied by Rourke and Ernstene.¹⁵

The hematocrit is filled to the "10" or "0" mark. For the determination of sedimentation rate the fall in the upper level of red cells is measured in millimeters by the calibrations and the numbers at the left of the scale (Fig. 2, A and B). There is considerable debate whether the single observation of the distance which the red cells have fallen at the end of 1 hour is an adequate test of the suspension stability of the red corpuscles. The instrument here described is, however, suitable for the "time," "distance," or "graphic" procedures.¹⁶ By means of an instrument devised in this laboratory,¹⁷ the sedimentation of the red corpuscles may be photographically recorded.

Determination of Volume of Packed Red Corpuscles. After sedimentation rate has been studied, in order to determine the volume of packed red cells the hematocrit is centrifugalized until no further packing occurs.

The time necessary for this may be readily determined for any centrifuge by a few trials. When the International centrifuge, size 1, type SB, head radius 9 cm., is used at a speed of 3000 r. p. m., packing is complete usually in 20 minutes and always in 30 minutes. Complete packing is, of course, essential, as otherwise considerable error may be introduced. If the hematocrit has been filled to the "10" or "0" mark, the proportion of packed red cells may be read directly. If potassium oxalate has been used as the anticoagulant in the quantity specified, the volume of packed red cells, as read, must be multiplied by the factor 1.09 to correct for shrinkage. If heparin has been employed no correction is necessary.

The determination of volume of packed red cells by the method here described is accurate to within 0.5 per cent.¹⁸ This probable error is less than that made in counting red cells even when the count is carefully carried out; and is much less than that of even the newer and more accurate methods of hemoglobin estimation.

The average volume of packed red cells for a large series of accurate determinations in healthy young men is 46 cc. per 100 cc. of blood, and in young women it is 41 cc. The variations for normal men and women are from 40 to 50 cc. and 37 to 45 cc., respectively. No large series of determinations has been made in older individuals, but the values which are available indicate that there is little or no change with advancing age as long as perfect health continues.¹⁹

Like either the red cell count or the hemoglobin value, the volume of packed red cells indicates the *degree of anemia or of polycythemia*. Neither the red cell count, the hemoglobin value or the volume of packed red cells is, however, alone a completely reliable index of the degree of anemia. As is well known, in certain types of anemia the red cell count may be normal when the hemoglobin and volume of packed red cells are even considerably reduced (microcytic anemias). In another type of anemia the red corpuscles are larger than normal and contain more than the normal amount of hemoglobin. In such cases the hemoglobin value and the volume of packed red cells may be normal when the red cell count is reduced. In pernicious anemia during a stage of incomplete remission such findings may be encountered. Again, although in the majority of anemias the amount of hemoglobin and the volume of packed red cells decrease or increase proportionately, in the hypochromic anemias the reduction in hemoglobin is even more marked than the decrease in the volume of packed red cells.

It is thus apparent that the volume of packed red cells is by itself no more certain an index of the degree of anemia, when all types are considered, than is the red cell count or the hemoglobin. Nevertheless, it may be considered equally important and, in view of the accuracy and ease with which it can be determined, in my opinion it *constitutes the most useful single criterion of the degree of anemia at present available*.

It has been the custom for many years to employ the red cell count and the hemoglobin as criteria of the *degree* of anemia, and the ratio between these, the color index, as a guide to the *type* of anemia. Many physicians have, however, lost faith in the color index because of the notorious inaccuracy of the commonly used methods of hemoglobin estimation and the great variety of standards employed as the equivalent of 100 per cent hemoglobin. The hematocrit fills an important gap in hematologic technique by making possible the calculation of the ratio between red cell count and volume of packed red cells, the information derived being essentially of the same significance and yet far more accurate than that afforded by the color index.⁷ This ratio between red cell count and volume of packed red cells may be expressed in the form of the volume index⁷ or the average volume of the red corpuscles may be calculated in absolute terms.²⁰ If the red cell count of the sample of blood used is known, the average volume of the red corpuscles (mean corpuscular volume) may be easily calculated by dividing the volume of

packed red cells, expressed in cubic centimeters per 1000 cc. of blood, by the red cell count, expressed in millions per cubic millimeter. The result gives the mean corpuscular volume in cubic microns. This method of expression is superior to the calculation of the volume index because, for the latter, certain standards of normality which must be arbitrarily fixed, are required.^{20,21}

When it is possible to estimate the hemoglobin accurately it is very useful to calculate the mean hemoglobin content of the red corpuscles (mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) as well as their volume.²⁰ Such information is of great value not only in differentiating anemias but also in indicating the type of treatment that may be expected to be effective. This subject has, however, already been discussed in some detail elsewhere²¹ and will, therefore, not be pursued here.

Determination of the Volume of Packed Leukocytes and Platelets. Another use of this hematocrit depends on the greater suspension stability of the leukocytes and platelets as compared with that of red corpuscles. When sedimentation is allowed to take place for an hour or longer in the hematocrit, the red cells become separated from the white corpuscles and platelets and, after centrifugation, the volume of packed leukocytes and platelets can be clearly distinguished from the volume of packed red cells.

In conditions in which the platelets and leukocytes are greatly increased in number, as in erythremia and sometimes in chronic myeloid leukemia, it is possible to secure by sedimentation and subsequent centrifugation a clear separation of all three corpuscles of the blood (Fig. 2, *G, H, I*). In such cases the platelets are found gathered together in a homogeneous cream-colored mass which constitutes the topmost layer (Fig. 2, *G, H, I*, and Fig. 3). The leukocytes form a homogeneous reddish-gray mass directly beneath the layer of platelets (Fig. 2, *G, H, I* and Fig. 4). Beneath the leukocytic layer is found the dark red layer of packed red corpuscles. The thickness of the layers of leukocytes and platelets may be taken as a rough measure of the quantity of these elements in the blood (Table 1A).

When the blood platelets are present in normal numbers they cannot usually be distinguished from the leukocytes. Under these circumstances only a reddish-gray layer is seen above the layer of packed red corpuscles. This reddish-gray layer (Fig. 2, *C, D, E, F*) is composed of both leukocytes and platelets (Fig. 5). In normal blood, when the hematocrit has been filled to the "10" mark, the reddish-gray layer is found to be 0.5 to 1 mm. in thickness (Fig. 2, *C, F*). That is, there is in normal blood 0.5 to 1 cc. of packed leukocytes and platelets per 100 cc. of blood.

When the platelet count is within normal limits the thickness of the reddish-gray layer corresponds very closely to the leukocyte count, each 0.1 cc. of reddish-gray material per 100 cc. of blood being equivalent to 1000 leukocytes per c.mm. The degree of accuracy

of this correlation is indicated by 103 observations recorded in Fig. 6. The correlation is greatest for counts up to 12,000, and is less exact for higher values. It may be noted, however, that in the majority of instances the correlation was sufficiently close to indicate leukocytosis when it was present and to give a rough index of its

TABLE 1.—VOLUME OF PACKED LEUKOCYTES AND PLATELETS.

*A. Leukocyte and Platelet Layers Distinguished.**

No. of observations.	W. B. C., average per c.mm. (thousands).	Volume packed W. B. C., cc. per 100 cc. blood.	Mean W. B. C. volume, c.μ.	Platelets, average per c.mm. (thousands).	Volume packed platelets, cc. per 100 cc. blood.	Mean platelet volume, c.μ.
3	16.1	1.6	990	547	1.7	31
3	23.0	3.2	1,390	860	1.1	13
5	34.8	3.0	810	870	2.6	30
5	44.2	2.9	660	567	3.2	56
3	54.3	2.9	540	1,040	2.4	23
1	60.7	4.6	760	1,080	2.5	23

* These observations were all made in cases in which the predominating leukocytes were granulocytes.

B. Cases in Which the Leukocyte and Platelet Layers Were Not Separately Distinguished.

Range of W. B. C. count (thousands).	Type of predominant cells.	No. of obser- vations.	W. B. C., average per c.mm. (thousands).	Platelets, average per c.mm. (thousands).	Volume packed W. B. C. and platelets, cc. per 100 cc. blood.
1.0 to 5	Myeloid	17	3.6	256	0.36
5.1 to 10	"	40	7.6	236	0.73
10.1 to 15	"	26	12.0	177	1.25
15.1 to 20	"	9	17.0	195	1.39
20.1 to 30	"	7	23.6	330	2.32
30.1 to 40	"	2	33.1	250	4.0
40.1 to 50	"	1	50.0	140	3.2
60.1 to 70	"	1	69.3	7.5
Above 200	"	1	228.0	134	10.0
Above 200	"	1	316.0	135	8.0
Above 200	"	1	950.0	46.0
10.1 to 20	Lymphoid	3	17.0	215	0.77
40.1 to 50	"	1	40.7	282	1.1
410 to 500	"	2	417.0	30	11.4
510 to 600	"	4	551.0	181	11.1
610 to 700	"	4	689.0	139	15.1

degree. As may be seen by examining Table 1, *B*, when the leukocyte count was excessively high, 0.1 cc. of packed leukocytes and platelets corresponded more nearly to 2000 leukocytes per c.mm. Furthermore, it is evident that when the predominating cells are lymphocytes, the factor given is incorrect, 0.1 cc. of reddish-gray layer corresponding in such instances approximately to 2000 leukocytes per c.mm. when the total count is relatively low (25,000), and to 4000 or 5000 cells when the count is high (40,000 or higher).

These observations are not recorded here with any object of presenting an easy method of determining the leukocyte or platelet count. The avenue of progress in hematology is in the direction of greater accuracy rather than in that of ready but rough procedures.

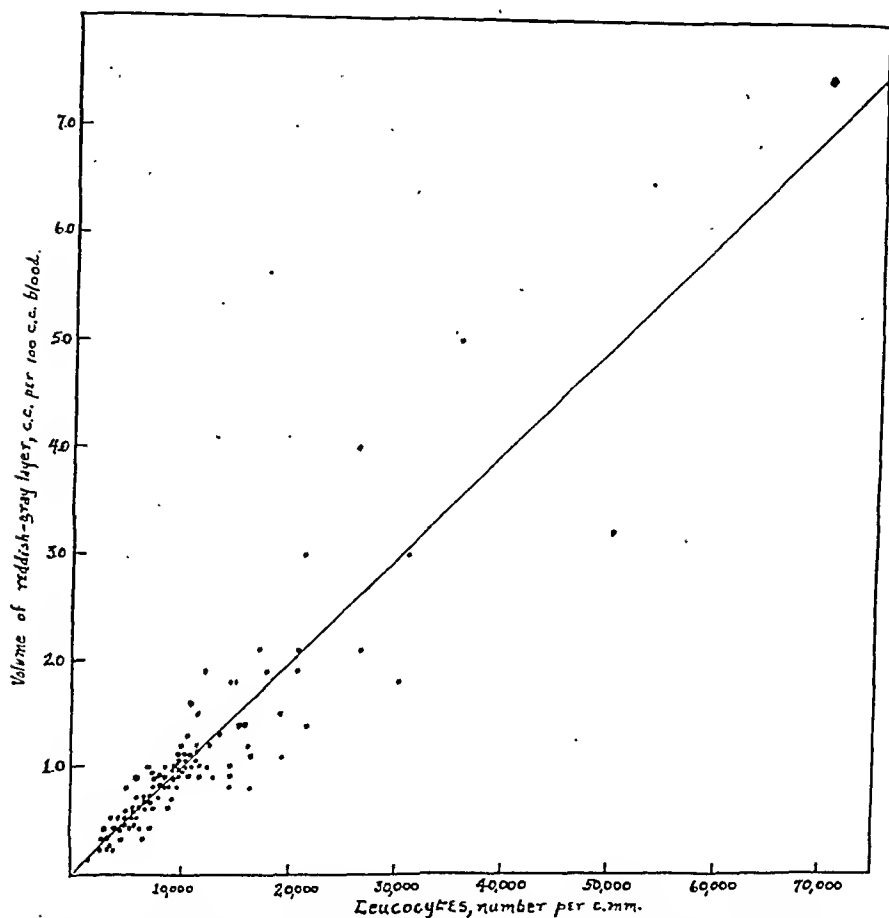


FIG. 6.—Correlation of volume of reddish-gray layer, consisting of packed leukocytes and platelets, to leukocyte count. Only those cases in which the predominating leukocytes were of the myeloid series and in which the platelet count was within normal limits, are included; 103 observations. The coefficient of correlation for the 100 observations in which the leukocyte count was 30,000 per c.mm. or less is 0.8582 ± 0.0178 .

Nevertheless, the thickness of the layer of packed leukocytes and platelets may serve, in the hands of experienced workers, as a useful rough guide to the quantity of these corpuscles in the blood. Thus, an extremely thin reddish-gray layer suggests leukopenia or, if the leukocytes are known to be present in normal numbers, it suggests thrombocytopenia. Again, when the layer above the packed red corpuscles is creamy in color rather than reddish-gray and yet not abnormally thick, one may suspect thrombocytosis and leukopenia.

On the other hand, as already mentioned, a thickened reddish-gray layer indicates leukocytosis, and from the thickness of this layer a fairly accurate estimate of its degree can be made.

If, in addition to the volume of packed leukocytes and of packed platelets, the number of leukocytes and platelets is known, it is possible to calculate their mean volume by a method similar to that followed in calculating mean corpuscular volume.²⁰ Our data show the average volume of the cells of the myeloid or granulocytic series to be 800 c. μ with the cells ranging between 500 and 1500 c. μ in size. In chronic lymphoid leukemia the lymphoid cells were found to vary between 170 and 300 c. μ . The mean volume of the platelets has ranged from 13 to 50 c. μ and averaged 30 c. μ (Table 1, A). At the present time this information is, however, of academic interest only.

Determination of Icterus Index. The measurement of icterus index has come into general use since the work of Meulengracht²² and of Bernheim.²³ It is now well known that, in the absence of liver disease, biliary obstruction and carotinemia, an increase in the yellow color of the blood serum or plasma is generally due to the presence of increased quantities of bilirubin resulting from increased blood destruction. Significant differences in the degree of bilirubinemia occur in the various types of anemia. Very commonly, however, in the cases of anemia in which hyperbilirubinemia occurs, this is not sufficiently great to be readily detected by physical examination alone. On the other hand, physical findings may be misleading for the pallor of the skin may be so great that it appears yellowish even when there is hypobilirubinemia. Such findings are not uncommon in chronic posthemorrhagic and in hookworm anemia. The estimation of icterus index is therefore of particular value in hematologic studies.²⁴

The measurement of the degree of icterus of the supernatant plasma in the hematocrit is the next obvious step in the use of this instrument. This has proved to be a most useful adjunct to the study of the blood.

For this purpose a comparator box* (Fig. 7) has been devised which holds a series of sealed tubes similar to the hematocrit as regards thickness of glass and inside bore. These tubes contain potassium dichromate solution in such dilutions as correspond to the icterus index units suggested by Murphy²⁵ and now generally employed. For the determination of icterus index, the hematocrit is placed, after centrifugation, in a special compartment in the comparator box and the comparator tubes are placed one on each side of it. A window permits only the upper, plasma-filled portion of the hematocrit to be seen. The comparator tubes are interchanged until one is found which matches the color of the blood plasma. The unit value is marked on each tube. It is particularly important when icterus index is to be determined that all apparatus used be clean and dry and that the blood be drawn before meals or some time after the taking of food, as otherwise lipemia may make the color matching difficult or impossible.

* Made by Arthur H. Thomas Company, Philadelphia.

Icterus index determinations by this method have been compared with values obtained by other techniques and have been found accurate. Blood serum is usually employed for the determination of icterus index by other methods, but we have found no differences between the icterus index values of serum and plasma.

The normal range of icterus index is usually considered to be 4 to 6 units. Values lower than 4 units indicate decreased blood destruction and are consistently encountered in chronic post-hemorrhagic and simple achlorhydric (hypochromic microcytic) anemia and, less frequently, in aplastic anemia and the simple microcytic anemia associated with chronic infections and intoxications. We usually hesitate to consider values of 7 or 7.5 units

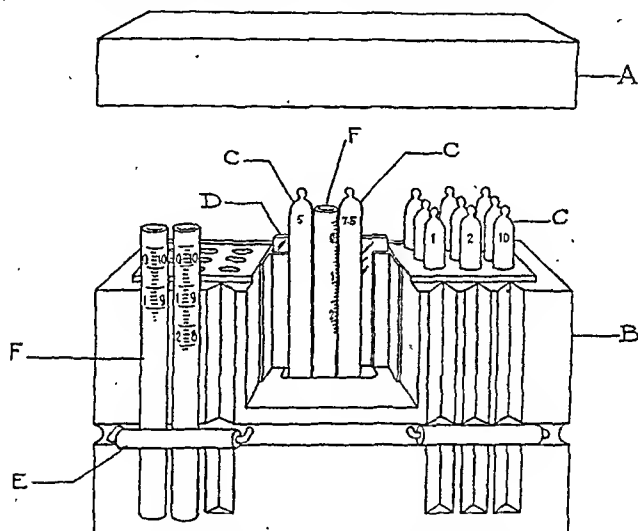


FIG. 7.—Icterus index comparator box and sedimentation rack. A, lid for box; C, icterus index standard tubes; D, blue glass; E, spring catch which holds hematocrits in position during sedimentation; F, hematocrit.

as significantly increased. Distinctly high values are characteristically found in sickle-cell anemia and in anemias caused by hemolytic agents such as malaria. In differentiating hemolytic from nonhemolytic types of anemia, the icterus index test is very valuable. In pernicious anemia the icterus index is characteristically greater than normal and is frequently high even when there is little or no anemia. In the latter instances hyperbilirubinemia and slightly increased mean corpuscular volume²¹ may be the only abnormal findings in the blood examination.

In interpreting the results of icterus-index determinations it must always be borne in mind that liver disease (even chronic passive congestion), obstruction of the biliary passages and increases in the lipochromes (lutein, carotin, and so on) of the blood, as occur following the ingestion of large quantities of eggs, oranges and chlorophyll-containing vegetables, cause an increase in the yellow color

of the blood plasma. It is very unusual for vegetables or eggs unless ingested in excessive quantities to influence the blood of adults but the ingestion of carrots, even as few as two, has been found to have a distinct effect on the blood.²³

When the icterus index test is employed in hematologic studies it must particularly be borne in mind that the absorption of blood from ecchymoses and hematomata such as are frequently encountered in the purpuras, both idiopathic and secondary (acute leukemia, aplastic anemia, etc.), may in itself lead to hyperbilirubinemia.

The Value of Examining the Appearance of Blood Plasma. As additional evidence of the value of gaining a macroscopic view of the blood may be cited two recent experiences. The first occurred in the course of our routine complete blood study in a case of Addison's disease. The plasma was found to be exceptionally cloudy, much more so than we had encountered in instances of post-prandial lipemia. Blood drawn again before breakfast revealed the same milky plasma. This accidental observation led to chemical studies which resulted in the discovery of chemical abnormalities in this patient's blood which had not previously been suspected.

A most unusual experience occurred in connection with a patient who complained of nosebleed, oozing of blood from the mouth, coldness, discoloration and pain in the extremities, and pain and swelling of the right shoulder joint. Physical examination made the diagnosis no less obscure. Blood examination, undertaken on account of the bleeding, revealed the presence in the hematocrit of cloudy plasma and a yellowish-gray layer 10 mm. in height above the layer of packed red cells. The finding of this gray layer which somewhat resembled the gray layer formed by leukocytes, was most surprising for it was already known that the leukocyte count and the platelet count were reduced rather than increased. Microscopic examination of the yellowish-gray material showed that it was made up of droplets of a brownish viscid substance which, on drying, crystallized. Furthermore, it was observed that the cloudy material in the plasma appeared on cooling and disappeared at room temperature. This variation with temperature put one in mind of the action of Bence-Jones protein and, in view of the associated anemia, leukopenia and thrombocytopenia a diagnosis of bone-marrow tumor was suggested. Subsequent examination and autopsy confirmed this suggestion. A detailed account of the observations in this case will be given elsewhere.²⁶

Summary. By a series of consecutive steps which are simple and may be quickly performed, it is possible by the use of a single instrument, a modified hematocrit, to gain accurate and valuable information concerning the blood.

1. Five cubic centimeters of blood are drawn from a vein with a dry syringe and needle and placed in a small bottle containing 10 mg. of potassium oxalate with which the blood is thoroughly mixed.

2. The hematocrit is filled to the "10" mark by means of a capil-

lary pipette and *sedimentation rate* is determined. The sedimentation rate serves as a guide to the presence and intensity of organic destructive or infectious disease.

3. The filled hematocrit is next centrifugalized until no further packing of the corpuscles takes place. The *volume of packed red corpuscles*, and the *volume of packed leukocytes and platelets* may then be read.

The volume of packed red cells is an accurate index of the degree of anemia and is more easily and more accurately measured than even the red cell count. It also serves to correct the sedimentation rate of the blood, as above determined, for the influence of anemia or polycythemia. Furthermore, if the red cell count and hemoglobin value of the sample of blood collected for hematocrit studies has been determined, the mean volume and hemoglobin content of the red corpuscles may be calculated. The latter information is of great value not only in differentiating the anemias but also in serving as a guide to the type of treatment which may be expected to be effective.

The volume of packed white cells and platelets serves as a rough guide to the quantity of these corpuscles in the blood.

4. Finally, the *icterus index* of the plasma may be read and this, in the absence of liver disease, biliary obstruction and carotinemia, serves as a useful guide to the degree of blood destruction.

Conclusion. The use of the hematocrit in the manner described affords, at the expense of very little time and effort, so clear and comprehensive and yet so accurate a macroscopic picture of the state of the blood, that its employment may well be considered in routine diagnostic studies. This method of employing the hematocrit is not recommended as a substitute for more detailed microscopic or chemical studies but, in experienced hands, it can be made to indicate along what lines the further study of the blood should proceed. This may well be the first blood study in those diagnostic clinics in which the technical personnel is too limited to permit the routine performance of erythrocyte, leukocyte and platelet counts as well as hemoglobin and van den Bergh tests.

My own experience with the hematocrit has convinced me that of the three instruments, the hemocytometer, the hemoglobinometer and the hematocrit, the last named affords more information concerning the blood than either of the other two, and indeed the information is more accurate. It is now my practice to use it in all diagnostic blood studies.

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BILATERAL CORTICAL NECROSIS OF THE KIDNEYS (ANGIONEUROTIC ANURIA).

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(From the Army Medical Museum. Publication authorized by the Surgeon-General,
U. S. Army.)

THIS strange pathologic entity has been the concern chiefly of the obstetrician, but the accumulation of at least 18 incidences where it has occurred in association with conditions entirely unrelated to pregnancy makes it the concern also of the internist. It is now obvious that Carson and Rockwood's¹ conclusion, written in 1926, that bilateral (symmetrical) cortical necrosis is invariably associated with pregnancy is no longer tenable, for the pathology is identical with the pregnant and the nonpregnant groups.

If the incidence of the condition be based solely on the pathologic anatomy, it will include only those patients who have died and whose kidneys show the orthodox picture of diffuse necrosis of the cortices. I accept the angioneurotic theory of the pathogenesis, however, and can assume that there is variation in the severity of the

vascular reaction. There are disturbances sufficiently severe to interfere with renal function but adjustable before the tissue is irreparably damaged. For the purposes of this paper, I have not gone so far as to include all the cases of nonobstructive anuria, but, as Scriver and Oertel² have done in their recent paper, I have accepted a number of cases with typical clinical pictures, but with deficient pathologic data. Bilateral cortical necrosis becomes a pathologic term under these conditions and indicates the terminal lesion. I suggest angioneurotic anuria as a clinical term applicable to all cases of nonobstructive anuria.

Scriver and Oertel's² excellent article includes references to 37 cases from the literature and 3 cases of their own. This is the largest collection to date. With the advantage of ready access to the Surgeon's-General Library, however, I have increased the number of reported cases to 60 and am adding 2 from my own experience.

In the attempt to discover heretofore unrecognized cases and to establish priority for the description of the condition, the following articles on eclampsia were reviewed: Leyden,³ the first to speak of the "kidney of pregnancy," King,⁴ Bouffe de St. Blaise,⁵ Schmorl,⁶ Lubarsch,⁷ Wienberger,⁸ Dürck,⁹ Petersen,¹⁰ Edebohls,¹¹ Franck,¹² Zinsser,¹³ Zangemeister,¹⁴ Goldzieher,¹⁵ Fahr,¹⁶ v. Fekete *et al.*,¹⁷ Hinselmann,¹⁸ v. Jashke,¹⁹ Zondek,²⁰ Fahr²¹ and Zangemeister's²² recent monograph. These articles include over 400 cases. In addition to these, 70 cases of anuria as reported by Cerou,²³ Merklen,²⁴ Neubürger²⁵ and Falci²⁶ were reviewed. It is probable that some of these were cortical necrosis, but none has been included in the series. One of Schmorl's⁶ cases, a woman, aged 35 years, who died with a clinical diagnosis of eclampsia, is particularly suggestive. He found infarcts of hyalin material in the capillaries and glomeruli, tubular thrombi in the arterioles and fat emboli in some of the glomeruli. He speaks of infarction, but he is not clear as to the distribution of the necrosis and he gives no clinical data. Lubarsch,⁷ Weinberger,⁸ Dürck⁹ and Peterson¹⁰ also describe fat emboli in the glomeruli, more or less thrombosis in the smaller vessels of the kidney cortex and the epithelium as varying from normal to completely necrotic. These data are suggestive, but are not sufficient to establish the cases as authentic. Kellogg,²⁷ in his study of the kidneys in cases with premature separation of the placenta, includes a group of 5 which showed partial or complete anuria. Only 1 of them was given in sufficient detail to warrant its inclusion, although the other 4 may have been equally acceptable.

The credit for the first recognizable pathologic description remains with Juhel-Rénoy.²⁸ There was a lapse of 12 years, however, before the lesion was established as a definite entity by Bradford and Lawrence's²⁹ case report.

TABLE 1.—SUMMARY OF 42 AUTHENTIC CASES OF BILATERAL CORTICAL NECROSIS ARRANGED CHRONOLOGICALLY.

Author ref. No.	Sex.	Age.	Basic clinical data.	Convulsions.	Headache.	Emesis.	Renal pain	Impaired vision.	Sys. blood pressure.	Edema.	Coma or drowsiness.	Number, days of anuria.		Albuminuria.	Nitrogen retention.	Remarks.
												Partial.	Complete.			
28	F	16	Scarlatina	+	..	+	+	..	Low	+	..	9	6	None.
29	F	36	Preg. VI	+	..	+	7	Almost	Normal pregnancy; drowsy, weak, postpartum.
52	F	30	Preg. V	+	..	+	188	10	Almost	Abdominal pain; convulsions day of death.
38	F	39	Preg. VII	+	..	+	140	11	Almost	Oliguria antepartum; hemorrhage.
53	F	35	Preg. V	+	..	+	11	6	Chronic nephritis; hemorrhage.
45	F	25	Preg. I	+	..	+	13	Almost	Cesarean; stupor just before death.
59	F	36	Eclampsia VII	+	..	+	13	Almost	Convulsions; decapulation, right.
56	F	22	Preg. 4 m. IV	+	..	+	15	6	Eclampsia; extremities cold and livid (Raynaud's?).
56	F	29	Preg. 7 m. IX	+	..	+	Low	8	Almost	Edema slight; "pulse low tension."
42	F	38	Preg. II	+	..	+	8	4½	Hemorrhage; dyspnea; urinous odor.
42	F	23	Preg. 4½ m. I	+	..	+	2½	Almost	Live twins.
42	F	23	Preg. 7 m. I	+	..	+	280	7	2	Eclampsia; hiccough; hematemesis.
37	F	23	Preg. XIII	+	..	+	115	1½	1½	Eclampsia; hemorrhage; decapsulation, bilateral.
57	F	48	Preg. I	+	..	+	8	8	Macerated fetus; abdominal pain; dyspnea.
47	F	22	Preg. I	+	..	+	3½	Almost	Eclampsia; premature.
48	F	35	Preg. 7 m. III	+	..	+	150	4½	4½	Eclampsia? fits antepartum; coma postpartum.
46	F	38	Preg. 8 m. I	+	..	+	4	Almost	Renal tenderness.
58	F	29	Camphor	+	..	+	4	4	Hemorrhage; renal tenderness; decapsulation.
50	F	14	Camphor	+	..	+	5½	5½	Camphor benzol, intrav. q. 2 h.; anuria 48 h. later.
50	F	48	Camphor	+	..	+	7	7	Bencke's case; cortical necrosis at necropsy.
42	F	46	Diphtheria	+	..	+	4½	4½	Toxemia; bilateral decapsulation.
49	M	37	Malaria	+	..	+	2	2	Suspected renal calculus.
38	F	33	Preg. 5 m. X	+	..	+	145	9	Almost	Spleen tender; dysenteric symptoms.
62	F	33	Preg. II	+	..	+	2	5	Old nephritis; abdominal pain; hemorrhage.
46	F	46	Preg. II	+	..	+	7	5	Eclampsia; Cheyne-Stokes breathing last day.
21	M	65	Ca. prostate	+	..	+	9	No clinical data; pathology cortical necrosis.
30	F	30	Preg. II	+	..	+	120	6	Almost	Normal until fourth day postpartum; decapsulation.
1	F	22	Preg. 6 m. VI	+	..	+	200	2½	Almost	Macerated fetus.
51	F	36	Rupture liver	+	..	+	150	12	0	Hemorrhage and shock.
41	F	38	Preg. 8 m. I	+	..	+	6	Almost	Abdominal pain; shock; hemorrhage; Cesarean.
63	F	29	Preg. 8½ m. I	+	..	+	170	5	1	Original reference not obtained.
40	F	34	Preg. 9 m. XV	+	..	+	170	5	9	Glycosuria; decapsulation; recovery.
39	F	29	Preg. II	+	..	+	8	Almost	Hemorrhage.
36	M	13	Tuberculosis	+	..	+	12	12	Detached placenta; macerated fetus.
31	F	37	Preg. 7 m. IV	+	..	+	118	12	Almost	Diarrhea and abdominal pain.
31	F	39	Preg. 7 m. III	+	..	+	120	12	Almost	Hemorrhage; macerated fetus; uremic odor.
34	F	24	Preg. 6½ m. III	+	..	+	20	6	Macerated fetus; dyspnea.
34	F	33	Preg. IV	+	..	+	117	11	11	Abdominal pain; Cesarean.
34	F	30	Placenta prev. I	+	..	+	150	5	5	Premature; abdominal pain; decapsulation.
32	F	38	Preg. 6 m. VIII	+	..	+	160	2½	2½	Hyperemesis; Cesarean.
55	F	38	Preg. VIII	+	..	+	24	24	Hemorrhage; anuria 2 days postpartum.

TABLE 2.—SUMMARY OF 18 PROBABLE CASES OF BILATERAL CORTICAL NECROSIS.

Author ref. No.	Sex.	Age.	Basic clinical data.	Convulsions.	Headache.	Emesis.	Renal pain.	Impaired vision.	Sys. blood pressure.	Edema.	Coma or drowsiness.	Number, days anuria.		Albuminuria.	Nitrogen retention.	Remarks.
												Partial.	Complete.			
54	F	13	Rheumatic heart	180	+	+	8½	8½	No clinical data; path. suggestive.
54	M	69	Ca. prostate	+	+	2½	1	Mentally clear; nephrotomy, right.
65	F	22	Hemiplegia	+	+	4	1½	Anemia; sudden onset; suggestive pathology.
37	F	31	Preg. V	+	+	9	0	Separation of placenta; Cesarean; no pathology.
44	F	38	Preg. I	160	+	+	17	0	Separation of placenta; recovered; no pathology.
33	F	..	Eclampsia I'	+	+	4	0	Cesarean; decapsulation, rt; recovered; biopsy.
33	F	64	Preg. 6 m. II	+	+	4	0	Labor induced; nephrotomy; recovered; biopsy.
47	M	10	Lobar pneumonia	+	+	Pathology suggestive.
47	F	10	Peritonitis	+	+	4	0	Abd. pain; laparotomy; pathology suggestive.
43	M	52	Renal colic	+	+	4	0	Decapsulation, lt.; anuria, rt., 14 days; recovered.
66	M	13	Polyarteritis	+	+	7	0	Abdominal pain; fever.
21	M	4	Dysentery	+	+	No clinical notes; pathology very suggestive.
21	M	56	Arteriosclerosis	+	+	13	13	Pathology suggestive.
31	F	25	Preg. III	+	+	Onset 6 days after delivery; nephrotomy, lt.; died.
60	F	43	Crushed chest	160	+	+	6	2	Died twenty-second day; rt. kidney necrotic.
27	F	40	Preg. 6 m.	220	+	+	37	Separation of placenta; Cesarean; recovered.
39	F	22	Eclampsia I	100	+	+	7	0	Living child; pathology suggests eclampsia.
2	F	37	Preg. 4 m. IV	+	+	Hypertemesis; hemorrhage; fluids forced; recovered.

In selecting the cases from the literature effort has been to avoid padding and some cases that were probably authentic were rejected arbitrarily, so that the collection may be regarded as a conservative representation. The pertinent data are given in Tables 1 and 2, the latter being a segregation of those cases to which exception might be taken.

My 2 cases are of particular importance because they were both males, apparently healthy until the sudden onset of the renal symptoms, and both presented kidney pathology as typically bilateral cortical necrosis as that seen in the pregnant women with eclamptic symptoms. Unfortunately, the clinical data are meager.

Case Abstracts. CASE 1.—A white soldier, aged 25 years, in good health, was seized suddenly with severe pain in the lower abdomen, nausea and vomiting on December 11, 1928. On admission to the hospital the same day his temperature was 102.2° F., his pulse 74 and respirations 20. It was suspected that he was suffering from acute appendicitis. He was given an enema, and food by mouth was stopped. The abdominal pain ceased on the second day in hospital, but he continued to vomit. Anuria became apparent at this time and the bladder was found empty on catheterization. A small quantity of urine obtained later contained albumin, hyalin casts and red blood cells. The vomiting persisted and increased in severity until his death, on December 29. For the last 2 days he had a constant diarrhea, and on the last day he developed air hunger and collapsed. There was no noteworthy change in his mentality nor did he have any convulsions. His blood pressure was 120 systolic and 85 diastolic after the onset, but no other readings were recorded. No estimation of urine secretion was made, but there was more or less complete anuria from December 12 to December 29, an unusually long period of 17 days. No blood chemistry determinations were made.

Pathologic Anatomy. The body was fairly well nourished and well developed. There was a punctate papular rash over the hands and feet, but no edema. The organs were considered normal except the kidneys. These were slightly enlarged and flabby, and the capsules stripped readily. Only formalin fixed tissues were received for examination, so that the details of the gross appearance were obscured. (Fig. 1.) In the broadened cortex, however, can be recognized the opaque, yellowish-white zone of necrosis with loss of normal markings and small, irregular, dark spots of hemorrhage. This necrosis extends almost to the capsular surface and to within a few millimeters of the pyramids, but it does not involve the columns of Bertini. It is defined from the more normal cortical tissue by a dark border of congestion. The pyramids stand out in contrast to the pale, turbid cortex, because of the dark streakings of their engorged vessels. None of the bloodvessels large enough to be seen grossly shows thrombosis or evidence of sclerosis.

Microscopic Appearance. The architecture and distribution of the lesion are well shown in the low power picture in Fig. 3. With higher magnifications, the following details are seen in the left kidney: In the narrow subcapsular zone the tubules are intact, although some of them are moderately dilated, and their epithelium is degenerated, usually hydropic. Some of the lumina contain desquamated cells, hyalin and necrotic debris and a few polymorphic leukocytes. These are not convoluted tubules, and the impression is that the material in them has come up from the necrotic zone. There are no intact glomeruli in this zone, nor is there any interstitial exudate to speak of. The bloodvessels are congested with

healthy red blood cells. This zone is interrupted by broad and narrow extensions of the completely necrotic zone to the surface of the kidney, and the inner limit is irregular from the projection into it of necrotic glomeruli and convoluted tubules.

There is a sharp transition into the zone of necrosis. Here there is scarcely a healthy cell to be seen, although the architecture can still be identified. There is considerable exudate, both interstitial and intratubular in the outer portions, but it also is necrotic and is present chiefly as pyknotic bodies and nuclear fragments. The epithelium of some of the convoluted tubules lying close to the larger intralobular* arteries takes the basic stain, indicating calcium deposit.

In the more central portions of this zone are large areas in which there is scarcely any evidence of a nucleus, and this only scattered fragments in the interstitial tissue. A hazy picture, in which the elements can scarcely be distinguished, except that the convoluted tubules stand out fairly prominently because their swollen, necrotic cells have taken the acid stain more deeply. The exudate increases again at the inner border of the necrotic zone. Some of the necrotic glomeruli and tubules project into the suprapyramidal zone and mingle with live elements, but there is no transition zone of partially necrotic structures.

The vessels in the necrotic zone are uniformly engorged and their walls necrotic, some disintegrated and invaded by leukocytes. Special staining shows the elastica in some of the vessels toward the periphery to be practically intact, in others disrupted or entirely absent. The intralobular arteries stand out prominently because of the layer of thrombus laid down on the intima, as shown in Figs. 5 and 6. This layer varies in thickness, but in no instance is the lumen entirely occluded. Phosphotungstic acid hematoxylin stain shows these thrombi to be composed of fused and hyalinized fibrin augmented by enmeshed conglutinated red cells, but no platelets can be recognized, nor is there any evidence of organization. The red blood cells in the remaining lumina of these intralobular arteries are usually discrete and well stained, but there is some conglutination in the larger masses. The tubular thrombi extend into many of the afferent arteries and end as plugs at the glomeruli. This is shown in Fig. 6. There is practically no thrombosis of the glomerular capillaries, except for the occasional extension of the thrombus in the afferent artery into a glomerular lobule. The red blood cells in the glomeruli and in the efferent arteries are usually discrete though pale, and they stain poorly with phosphotungstic acid hematoxylin. They are evidently older than those proximal to the thrombi. The smaller interstitial vessels are engorged but not thrombosed, and there are no thrombi outside the necrotic zone. There are large arteries at the inner border of this zone that are not thrombosed, although their walls are necrotic. Small, recent hemorrhages, some of which are from ruptured glomeruli, others from leakage through the necrosed walls of bloodvessels, are scattered through the center of the necrotic zone.

In the suprapyramidal cortex there is some apparently recent increase in the interstitial connective tissue adjacent to the necrotic zone. There is a moderate generally distributed interstitial edema, and a small amount of exudate. The bloodvessels are congested and some of them contain bacterial masses. These are agonal and of no etiologic significance, for they are seen also in the vessels of the spleen, liver and pancreas without any reaction referable to their presence. Several of the glomeruli are engorged with healthy blood, but otherwise they are normal. The epithelium of the tubules is well preserved, but there are many casts and considerable debris in the tube lumina.

* Gross's terminology is used. Intralobular arteries are the interlobular, and the interlobar are the arcuate arteries of the older terminology.

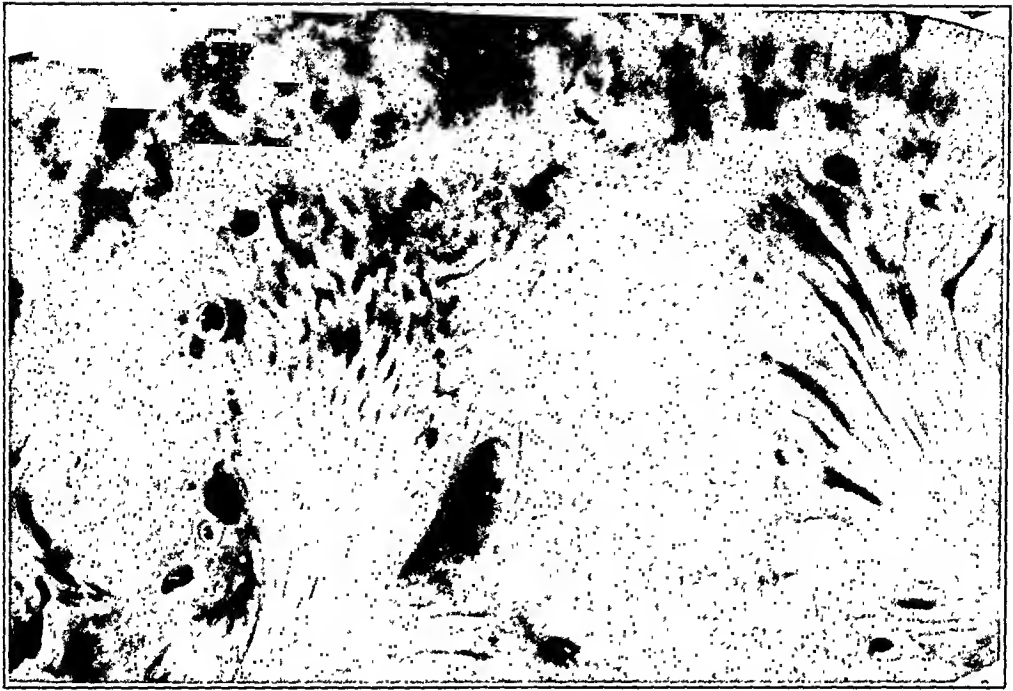


FIG. 1.—(Case 1.) Cortex necrotic and mottled with hemorrhages; thrombosis of intralobular arteries; columns of Bertini and suprapyramidal zones comparatively uninvolved; medulla congested; large vessels patent. A. M. M. Neg. 49423. ($\times 1\frac{1}{2}$.)



FIG. 2.—(Case 2.) Necrotic zone of cortex outlined by shaded zone of congestion and exudate in which intralobular arteries are thrombosed. Medulla congested. A. M. M. Neg. 49410. ($\times 9$.)

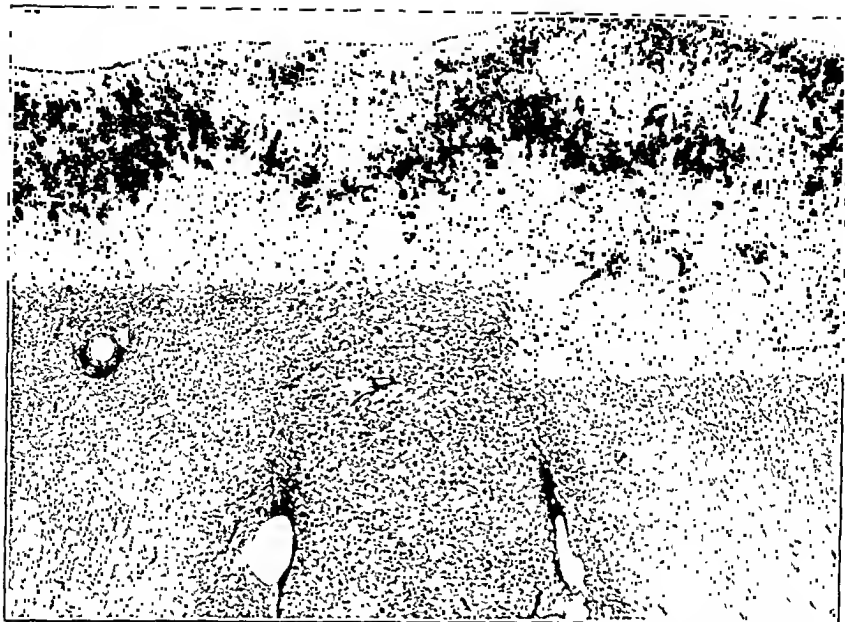


FIG. 3.—Section of kidney from Case 1 stained with phosphotungstic acid hematoxylin, which emphasizes the zone of congestion and exudate and the thrombi. The non-necrotic subcapsular zone can be recognized readily. A. M. M. Neg. 49442. ($\times 8$.)



FIG. 4.—(Case 2.) Kidney from Case 2. Same stain as Fig. 3. A comparatively free strip of cortex extends to the capsular surface. The free subcapsular zone is broader than that in Fig. 3. A. M. M. Neg. 49446. ($\times 9$.)

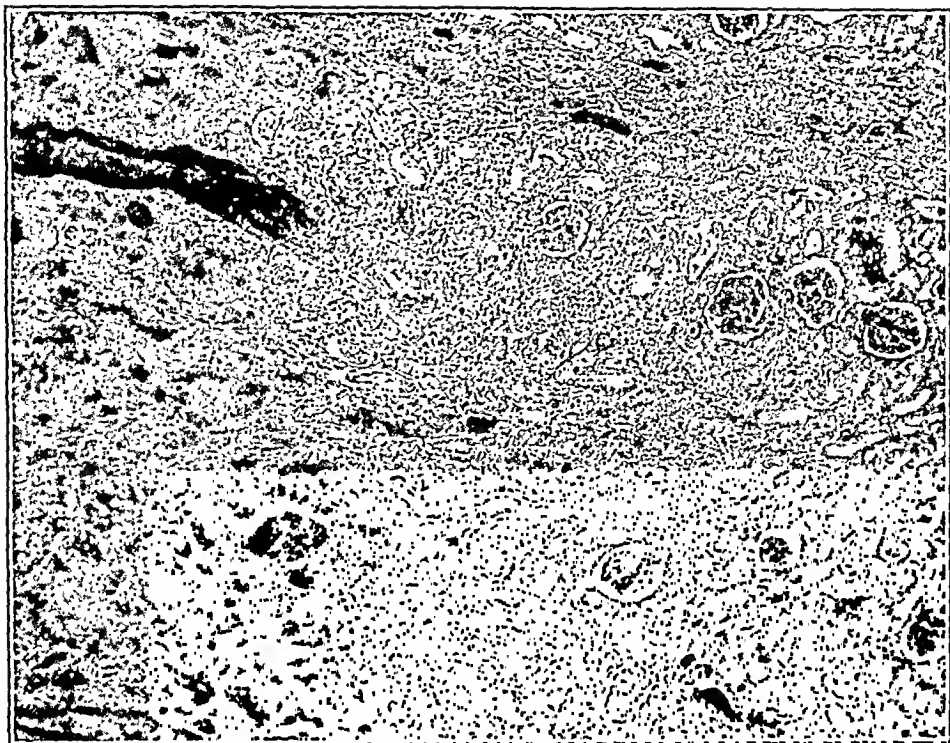


FIG. 5.—(Case 1.) Suprapyramidal free zone to the right; zone of complete necrosis to the left; intervening zone of exudate and irregular necrosis. A widely dilated and necrotic intralobular artery contains a tubular thrombus. A. M. M. Neg. 49413. ($\times 45$.)

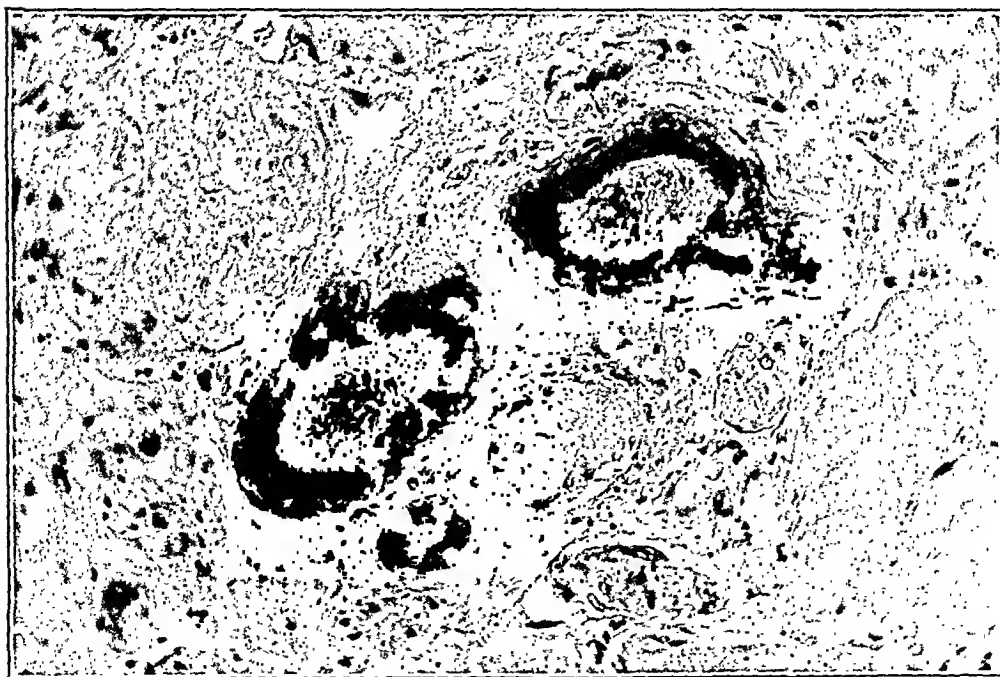


FIG. 6.—(Case 1.) From the necrotic zone near the subcapsular area. Tubular thrombi in necrosed intralobular arteries. Glomeruli engorged but not thrombosed. Some of the nuclear fragments may represent old exudate. Interstitial edema. A. M. M. Neg. 49415. ($\times 200$.)



FIG. 7.—(Case 2.) Thrombosis of afferent arteriole; glomerular capillaries distended with partially laked red cells. Necrosis of all structures with preservation of architecture and absence of exudate. A. M. M. Neg. 49406. ($\times 310$.)

The large collecting tubules of the pyramids are filled with casts, exudate or necrotic debris, although their epithelium shows little change. Some of the epithelium of Henle's loops is swollen and granular, but generally it is not much altered. The lumina usually contain more or less granular and hyalin debris. The vessels are engorged, but the walls show no damage. There is some interstitial edema, and extending up from the pelvic mucosa are broad streaks of chronic exudate consisting of polymorphic leukocytes, lymphocytes, a few plasma cells and eosinophils. Similar exudate is found in the pelvic fat. Beneath the pelvic mucosa there is some hemorrhage, and the exudate contains a larger proportion of polymorphic leukocytes. The large vessels at the hilus do not show any noteworthy change. The distention of the interlobar vessels can be seen in Figs. 2 and 3.

The right kidney presents a similar picture, except that there is more exudate in the pre-necrotic zone, but fewer hemorrhages and less thrombosis.

The thrombi do not show the tubular arrangement so strikingly.

In addition to the bacterial masses in the vessels of the spleen, pancreas and liver, the latter contains a few fat droplets in the cells of the central zones, and the pancreas is the seat of postmortem change.

CASE 2.—A white army officer, aged 32 years, who likewise gave no previous indication of anything wrong, was seized with nausea and vomiting on July 22, 1928. He was admitted to the hospital, July 24, complaining of pain over the entire abdomen and extreme tenderness over both kidneys. The following day he complained of inability to void. He was catheterized and 10 cc. of "thick" urine containing albumin, and hyalin and granular casts were obtained. There was almost complete anuria for the first week, and during the following 12 days until his death, August 12, he passed from 120 to 150 cc. of dark urine per day. Each specimen contained albumin and casts. His temperature for the first 2 days in the hospital was 99.5° to 100° F., following which it was normal or subnormal. The nausea and vomiting were persistent, but he had no convulsions nor mental disturbance. There is no record of the blood pressure nor of blood chemistry determinations.

Pathologic Anatomy. (Autopsy limited to abdomen.) The body was well developed; there was no superficial edema. The peritoneal cavity contained 1 liter of straw-colored fluid. The kidneys were both enlarged, tense and their capsules stripped readily. In this case also were received only pieces of the kidneys that had been fixed in formalin. The distribution of the necrosis, however, can be seen in Fig. 4. The subcapsular zone is broader than that in Case 1, but the necrotic zone is also deeper and it involves the columns of Bertini. In this case there are strips of nonnecrotic cortex extending from the pyramids to the capsular surface, interrupting the necrotic zone. The large vessels are free.

A piece of small intestine was the only other tissue received, and it shows a moderate hyperemia with some postmortem desquamation of its epithelium. Except for minor variations, the kidneys present the same picture as do those of Case 1. The necrosis was even more sharply defined and more extensive. The necrotic zone looks as though it were unfixed tissue that had been in water for a long time. There is less thrombosis of the larger vessels, although the plugging of the afferent arteries at the glomeruli is as frequent.

Clinical Summary. SYMPTOMS. The important symptoms are summarized in Tables 2 and 3. This can be done only approximately, and no percentage estimation of the occurrence of the various symptoms is possible, because of the meagerness of data in the majority of the case reports. It cannot be assumed that a symptom was absent simply because it was not noted.

One is impressed by the comparatively mild clinical picture, especially in those cases not complicated by eclampsia nor by the toxemia of pregnancy. In several incidences the symptoms improved decidedly after the uterus had been emptied, in spite of the anuria. There was a distinctly lower incidence of convulsions, headache and edema than one sees in uremia, and there was much less mental disturbance. A number of the patients were perfectly clear mentally until a few hours before death. The picture is much the same as that resulting from obstruction of both ureters, or from bilateral nephrectomy.

Anuria, partial or complete, is the only symptom common to all the cases. It may appear without any premonitory symptoms of kidney damage, or it may follow a normal pregnancy with uneventful delivery, as illustrated by the cases reported by Bradford and Lawrence,²⁹ Hirst³⁰ and Iungano.³¹ It varies in duration and degree from 1 day of complete suppression to several weeks of diminished flow. In the majority of cases the duration has been 8 days or less. Iungano's³¹ patient apparently holds the record with 13 days of complete anuria, with Dalrymple's³² case second with 11 days. There have been several instances of partial suppression for longer periods, however. One of White's³³ patients recovered after 17 days; Case 4 of Davidson and Turner³⁴ lived 20 days, during 6 of which anuria was complete, and both of my patients survived for unusually long periods, 15 and 19 days, respectively.

Diarrhea was a noteworthy symptom in several cases, sufficiently severe in Bainforth's³⁵ to suggest dysentery. Apert and Bach³⁶ speak of it particularly in their boy with tuberculosis, and it was a terminal symptom in my first case. It may have represented an attempt at compensatory elimination of fluids.

Blood pressure is mentioned in 23 cases, in 14 of which it is well within normal limits. The highest is reported by Couvelaire,³⁷ a pressure of 280 mm. Hg in a primipara with eclamptic symptoms in addition to the anuria. In 3 instances of high pressure there was a reduction following the emptying of the uterus. In Lloyd's³⁸ case it dropped from 188 to 120; in Carson and Rockwood's,¹ from 200 systolic and 130 diastolic to 170 systolic and 110 diastolic; in Westman's³⁹ second case, from 200 systolic and 150 diastolic to 130 systolic. The high readings were all recorded in pregnancy complicated by eclampsia or placental hemorrhage. Apparently the anuria *per se* did not affect the blood pressure materially.

A definite *nitrogen retention* is reported in 12 cases. As might be expected, it was greatest in the eclamptics. Crook's⁴⁰ case showed a total blood nonprotein nitrogen of 388 that returned to normal after kidney decapsulation. The highest blood creatinin was reported by Manley and Kliman,⁴¹ 12.5. As may be seen in Table 3, the 5 records of creatinin are all high. Scriver and Oertel² call attention to this rapid accumulation in cortical necrosis, and

contrast it to the slower rise seen in chronic nephritis and in chronic urinary obstruction, as from carcinoma of the prostate.

TABLE 3.—BLOOD CHEMICAL FINDINGS IN 10 CASES OF BILATERAL CORTICAL NECROSIS.

Author.	Nonprotein nitrogen, mg.	Urea nitrogen, mg.	Creatinin, mg.
Kellogg	100		
Hirst	106	7.0
Manley and Kliman	75	12.5
Crook	388*	
Westman	71	
Apert and Bach	290	
Dalrymple	300		
Scriver and Oertel	6.6
Scriver and Oertel	6.4
Scriver and Oertel	104*	..	6.0

* Returning to normal.

Urine. The 22 cases in which urinalyses were recorded showed albumin; the majority of the specimens contained casts and 5 of them blood.

DIFFERENTIAL DIAGNOSIS. This depends almost entirely on the interpretation of the anuria. The latter may be a feature of several other conditions, especially nephritis, hysteria, poisons and general dyscrasias, but renal infarction and bilateral ureteral occlusion are the two important conditions which must be excluded before making the diagnosis of bilateral cortical necrosis. As has already been mentioned, the clinical picture presented by cortical necrosis resembles closely that seen in obstructive anuria, particularly in the mildness or absence of uremic symptoms. The differentiation, of course, depends on a careful urologic examination to determine the patency of the urinary tract.

The differentiation of cortical necrosis from renal infarction may not be so easy. Sudden onset, nonradiating renal pain, albuminuria, hematuria and oliguria are common to both. But, while renal pain was mentioned in only 11 cases of cortical necrosis, it is a constant and prominent symptom in renal infarction of sufficient extent to interfere with urinary output. Anuria, on the other hand, is not so constant a feature of infarction, nor is it so likely to be complete as it is in cortical necrosis. Infarction is usually an accident of cardiovascular disease, so that the history of the patient and a general physical examination are important.

Jardine and Kennedy⁴² think that it is impossible to differentiate cortical necrosis from chronic nephritis complicating pregnancy.

PROGNOSIS AND TREATMENT. In its strictly pathologic sense bilateral cortical necrosis must be considered invariably fatal. So much of the essential tissue is destroyed that the process is equivalent to a bilateral nephrectomy. There is no evidence that the necrosis is ever sufficiently limited to leave enough functioning parenchyma to sustain life, as is the case in infarction.

If, however, we use the term in its broader sense, accepting the vasomotor theory of pathogenesis, we may include cases that recover. There are 7 of these in the 62 cases of this series. They did not have the pathological entity of bilateral cortical necrosis. In White's³³ 2 cases, and Crook's⁴⁰ single case, all of which recovered, the biopsy specimens did not show the necrotic stage of the condition, and we must conclude with White, that the necrosis is the terminal stage of the process.

There seems to be no way, however, of determining clinically in what stage of the pathologic process a given case may be, for the symptoms were just as severe in the patients who recovered as in those who died. We can assume that those who recovered did not have extensive necrosis, but we cannot say with assurance that any treatment they received prevented its development. In several instances, however, there was evidence of a favorable influence from treatment, and I cannot agree with those who believe that all treatment is hopeless. Pal's⁴³ experience is particularly significant. After decapsulation of the *left* kidney of a man who had had a complete anuria for 4 days the daily urinary output increased to 1800 cc., but the *right* kidney remained anuric for 2 weeks. Crook's⁴⁰ patient, who had been anuric over 4 days, passed 33 ounces of urine during the day following the decapsulation of her right kidney, and she eventually recovered. Experiences of this sort are of greater significance in evaluating the influence of treatment than the fact that only 4 recovered of the 13 patients on whom decapsulation or nephrotomy was performed; for the pathologic examination of those who died showed that necrosis had already developed at the time of the operation. Edebohls,¹¹ who first suggested the operation of decapsulation, in 1904, reported the recovery of 3 cases of oliguria in eclampsia following his operation, and Franek,¹² in 1907, collected 10 cases of which 6 recovered. It is with the hope, therefore, of possibly aborting the process in the pre-necrotic stage that operation is advocated. White³³ recommends as a routine procedure the splitting of the kidney capsules during a Cesarean section on eclamptics with oliguria.

On the other hand, the 3 additional recoveries in my collection reported by Kellogg,²⁷ Seriver and Oertel² and Oldfield and Hann,⁴¹ had no kidney operation, but were treated with glucose and the forcing of fluids. Kellogg²⁷ is a particular advocate of this form of treatment on the theory that the maintenance of a high blood pressure favors reestablishment of the circulation through the engorged renal vessels. He particularly condemns decapsulation.

Dalrymple,³² assuming that the process results from toxins, advocates the plasmapheresis of Irving and Taylor.

PATHOLOGIC ANATOMY. There is a noteworthy uniformity in the lesions of the kidneys in the authentic cases. The variations are minor ones, often depending on differences in interpretation. The

picture resembles roughly that of an anemic infarct, except for the peculiar distribution, less extensive hemorrhage and strikingly greater engorgement of the vessels in the necrotic areas. Hemorrhages and exudate have been mentioned by several authors, but they are not constant. Calcium deposit in the necrotic cells as seen in my first case is mentioned by Klotz,⁴⁵ Geipel,⁴⁶ Iungano³¹ and Scriver and Oertel.² The last two observers also found large quantities of fat, not only in the necrotic cells, in which it is common, but in the tubular and vascular lumina, a unique feature in this series of cases. But the chief variation is in the discussion of the thrombi, their composition, point of origin and distribution. While the reports are practically unanimous in limiting them to the necrotic zone, Herzog⁴⁷ and Schüppel,⁴⁸ for example, believe that they begin in the glomeruli or afferent arteries and extend centrally, while Geipel⁴⁶ and Westman³⁹ believe they originate in the larger cortical vessels and extend peripherally. Several of the authors confirm the finding in my 2 cases of the frequency of occluding plugs in the afferent arteries at their entrance into the glomeruli. Stöckenius⁴⁹ speaks of it particularly. The majority, also, have noted the scarcity of thrombi distal to the afferent arteries. The thrombi have been described as being composed of blood platelets, fibrin, conglutinated red blood cells and combinations of these. While these discussions are interesting, one is forced to conclude that the thrombosis is, after all, not the cause of the lesion, but that it is a secondary feature. In 14 of the 44 authentic cases thrombi were either not mentioned or they were too few and scattered to have been the primary cause of such extensive necrosis.

There is one interesting and important feature of the pathology that must be emphasized. The duration of the anuria seems to make little difference in the terminal picture. The same degree of necrosis and thrombosis is described in those cases which have died after a few days of anuria as is seen in those which have lived 8 or 10 days. Zanzig,^{*50} for example, describes extensively necrotic cortices with all of the cortical vessels filled with thrombi in the kidneys of a girl, aged 14 years, who died after 4 days of anuria following camphor injections.

Furtwängler⁵¹ describes practically complete cortical necrosis that must have developed within 60 hours after an automobile accident, in which the liver was ruptured but in which the kidneys were not directly injured. It is true that organization and fibrosis have been mentioned in a few instances. Zaaijer⁵² describes granulation tissue in the kidneys from his patient who died after 10 days of

* This author has been referred to as "Zunzig" by several writers, the last, in 1927. His Dissertation, unfortunately, is not indexed in the Index Medicus, the Cumulative Index or the Catalogue of the Surgeon-General's Library. It was only after considerable search, therefore, that the original was located in the Surgeon-General's Library.

almost complete anuria, and Griffith and Herringham⁵³ found an increase of the interstitial tissue in their case who died after 11 days of anuria, but this fibrosis was very likely an evidence of the chronic nephritis for which she had been under treatment for some years. But it does seem that if the thrombosis and necrosis were responsible for the anuria, there would have been more evidence of an attempt at organization and repair than has been reported in the 22 cases in which the anuria lasted for 8 days longer.

ETIOLOGY. From the clinical data presented, it will be seen that of the 44 authentic cases, 34 complicated pregnancy, 2 followed the intravenous use of camphor, 3 were of cryptogenic origin and 1 occurred in each of the following conditions: scarlet fever, diphtheria, carcinoma of prostate, pulmonary tuberculosis and trauma. Of the 18 cases about which there may be some question, 8 were in pregnancy, and 1 each in dysentery, carcinoma of the prostate, rheumatic fever, anemia, lobar pneumonia, polyarteritis nodosa, arteriosclerosis, acute peritonitis, trauma and 1 was of cryptogenic origin.

Seven of the 62 patients were children, the youngest a boy, 4 years (Fahr²¹), and the oldest a girl, aged 16 years (Juhel-Rénay²⁸). The oldest patient of the series was Weber's,⁵⁴ a man, aged 69 years, with carcinoma of the prostate. Of the 20 which did not occur in pregnancy 7 were females and 12 were males. The sex of 1 was not stated. The only significant feature of the distribution in age and sex is that the 4 cryptogenic cases were adult males.

These 4 cases are of particular interest, for they establish the fact that cortical necrosis can develop in the absence of obvious disease.

In only 2 cases was trauma involved, but that it is a more important factor than these 2 selected cases would indicate is evidenced by Cerou's²³ Merklen's²⁴ and Neubürger's²⁵ reports of anuria lasting from 18 hours to 14 days, only 1 of the patients surviving.

There are 42 instances of cortical necrosis occurring in pregnancy. Twelve of them were primiparas and 27 multiparas of from 2 to 15 para. In 3 cases the number of pregnancies was not recorded. Twenty-one of the patients were over 35 years of age, the oldest being 48 years, and 12 were under 30 years, 3 of these being but 22 years. There is, therefore, a higher incidence in multiparas over 35 years of age.

In only 7 patients did the cortical necrosis occur at full term, and only 4 were delivered of living children. These last cases were reported by Jardine and Kennedy⁴² (twins), Immink,⁵⁵ Westman³⁹ and Lungano.³¹ In 7 instances it was stated that the fetus was macerated.

In only 11 cases was the pregnancy uneventful before the onset of the anuria. Of the others, 20 had had uncomplicated edema, 17 evidence of renal damage and 9 had been diagnosed eclampsia.

Spontaneous abortions, induced labors, Cesarean sections are frequently mentioned in the reports. Scriver and Oertel² attach significance to the fact that there was retroplacental hemorrhage in 13 cases.

That the anuria may be a delayed phenomenon is evidenced by Lungano's³¹ case in whom it did not occur until 13 days after a normal delivery, by Hirst's³⁰ with a delay of 4 days and by Jardine and Kennedy's⁴² in whom it developed several days after a therapeutic abortion.

In order to explain the uniform picture seen in the kidneys from this series of cases, it must be assumed that there is some factor or combination of factors that are common to at least the many clinical conditions cited above. It is obvious, also, that either this factor is more commonly present in pregnancy than in any other clinical condition, or pregnancy affects the kidneys in some way to make them more sensitive to it. It is not surprising, therefore, that so much of the discussion in the literature is concerned with pregnancy, and that every real and hypothetical condition incident to pregnancy has its advocates as an etiologic factor. But while increased coagulability of the blood, alterations in blood pressure, specific toxins originating in the placenta (the dead fetus or otherwise) and affecting the vascular endothelium or the renal epithelium, ischemia from pressure, emboli originating in placenta, liver or from the fatty tissues may be factors determining the relatively high incidence of cortical necrosis in pregnancy, they cannot be accepted as immediate instigators of the process. At present there are not enough data to indicate just what does cause the condition.

PATHOGENESIS. With the cause unknown, there must be, also, divergence of opinions as to the mechanism producing the lesions. The extent and distribution of the necrosis eliminate emboli as the first step in the process. Juhel-Rénoy²⁸ was the only advocate of this theory. Zaaier⁵² thought that increased intrarenal pressure could compress the less resistant afferent arteries sufficiently to cause necrosis of the large portion of the cortex which they supplied. Pal⁴³ and White³³ advance a somewhat similar hypothesis. Weber,⁵⁴ Hirst,³⁰ Manley and Kilman,⁴¹ Bamforth³⁵ and Kennedy⁴² look upon the epithelial damage as primary and the thrombosis secondary. Crook⁴⁰ suggests that interference with metabolism and with water elimination, probably through disturbed pituitary influence, may affect the kidneys sufficiently to cause the necrosis.

The other authors can be divided roughly into two schools. Bradford and Lawrence,²⁹ Lloyd,³⁸ Griffith and Herringham,⁵³ Klotz,⁴⁵ Torrens,⁵⁶ Rolleston,⁵⁷ Herzog,⁴⁷ Schüppel,⁴⁸ Geipel,⁴⁶ Glynn and Briggs,⁵⁸ Stöckenius,⁴⁹ Carson and Rockwood,¹ Westman,³⁹ Davidson and Turner³⁴ and Dalrymple,³² all regard the process as primarily a thrombosis, attributing it variously to toxic damage

of the vascular endothelium, qualitative blood changes that increase the coagulability, altered intrarenal blood pressure or a combination of these factors.

Jardine and Teacher,⁵⁹ Zanzig,⁵⁰ Furtwängler,⁵¹ Immink,⁵⁵ Fahr,²¹ v. Marenholtz⁶⁰ and Kellogg²⁷ belong to the other school which holds that the first step is a spasm of cortical vessels. It is interesting to note that Cerou,²³ writing in 1877, and Merklen,²⁴ in 1881, explain the anuria following trauma and burns as the result of reflex vasoconstriction, basing this opinion on Claude Bernard's and Bulpin's investigations of the reflex nerve influence on the vascular supply of the kidneys and on urinary secretion. Neubürger²⁵ explains the gross infarcts which he found after trauma as due to the spastic closure of branches of the renal arteries, the result of strong mechanical irritation, and Zangemeister²² ascribes the lesions of eclampsia to focal angiospasm. In Scriver and Oertel's² recent article Oertel discusses convincingly the vasomotor origin of the phenomenon. Basing his interpretation of the lesion largely on the studies of Ricker⁶¹ on the response of vascular elements to various degrees of irritation, he considers it after all "the results of irritations of arterial terminal segments of different intensities." In the terminology of Ricker, the zone of dilated arterioles and capillaries and of exudate represents "peristasis," the zone of vasoparesis and hemorrhage represents "prestasis" and the necrotic zone with complete cessation of blood flow is the final stage of vessel collapse "stasis." Oertel tends to emphasize the vasostasis, and it certainly is a striking feature of the picture, but he acknowledges the possibility that the primary reaction to the "irritant" may be vasoconstriction.

The experiments of Colnheim, Lubarsch, Litten and others have shown that an ischemia of about 2 hours' duration is sufficient to produce necrobiosis in the kidney, and that this time is materially shortened if the ischemia is complicated by a toxemia. Perhaps this toxemia is furnished by pregnancy or the other clinical conditions, including the shock of trauma. These conditions may contribute also to the formation of the thrombi. The evidence indicates that the thrombosis is secondary, not to the necrosis, as some would claim, but to the stasis. The thrombi begin in the afferent arteries and extend in a proximal direction to the limit of the necrosis, so that they rarely go beyond the interlobar arteries. They are rare in the glomeruli, efferent arteries and veins. The blood in these vessels is "stale" and so may have lost some of its coagulability. The exudate does not indicate a primary inflammatory reaction as much as it does the reaction to necrotic tissue.

Summary and Conclusions. 1. Sixty-two cases of bilateral cortical necrosis of the kidneys selected from the literature and 2 added from personal experience have been analyzed.

2. The condition occurs most commonly in pregnancy, but is seen also in a variety of infectious diseases; it may follow trauma and it may develop cryptogenically. The pathology and pathogenesis are the same under any of these conditions.

3. Bilateral cortical necrosis is a pathologic term applicable only to the terminal stage of certain cases of nonobstructive anuria. It is recommended that "angioneurotic anuria," therefore, be adopted as a clinical term to include all nonobstructive anurias.

4. Treatment is of no avail in the pathologic condition "bilateral cortical necrosis," but there is evidence that decapsulation of the kidneys or nephrotomy will favorably influence an otherwise refractory angioneurotic anuria.

5. The immediate cause or causes of bilateral cortical necrosis are not known, but in my opinion it is most probable that the anuria is the result of vasomotor disturbance, probably a vasoconstriction that is followed by vasoparalysis and stasis, and that the striking picture of necrosis and thrombosis found post-mortem is relatively terminal. Depending on conditions which are not understood, these terminal lesions may develop after a few hours of anuria, may be deferred for days or may not develop at all. In the last circumstance the patient may recover.

NOTE.—I wish to express my gratitude to Prof. Howard T. Karsner and his assistants at the Pathologic Institute of Western Reserve University, Cleveland, for assistance in identifying the lesions in Case 1, to Dr. Neuman and Mr. Toepper, Assistant Librarians at the Surgeon-General's Library, for their generous aid in tracing ambiguous references, and to Major Paul E. McNabb, Curator of the Army Medical Museum, for seeing the manuscript through the press during my absence on foreign service.

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THE SIGNIFICANCE OF THE LARGE Q WAVE IN LEAD III.

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THAT the *Q* wave in Lead III may become large in coronary occlusion was noticed by Pardee¹ and later by Parkinson and Bedford² and Levine.³ Pardee⁴ lately offered criteria for defining the large *Q* wave in Lead III and called attention to the fact that the majority of such records are obtained from patients with the anginal syndrome. Willius,⁵ in reviewing his records, finds that this abnormality in the electrocardiogram is by no means limited to the anginal syndrome, but seems to occur in diseases exerting their influence chiefly on the left ventricle. Fenichel and Kugel⁶ recently studied the correlation of such electrocardiograms with pathologic findings and concluded that the large *Q-3* is the most frequent electrocardiographic finding of coronary artery disease during the chronic stage, and that the large *Q-3* in myocardial infarction and fibrosis is probably due to the involvement of the posterior portion of the septum. These observations stimulated us to investigate the electrocardiographic tracings in our files.

Material. The files in the electrocardiographic laboratory contain tracings not only of patients from the Cardiac Clinic, but of patients from other clinics as well. A number of these patients have no organic heart disease, hence our records represent not only a variety of cardiac patients, but also a fair number of normals.

Seventy-five of the 2000 electrocardiograms carefully studied were found to conform with the qualifications set forth by Pardee,⁴ namely: (1) In Lead III a downward initial deflection (*Q*), succeeded by a definite upward deflection (*R*), with no (*S*) following. (2) An excursion of the *Q* wave in Lead III of more than 25 per cent of the greatest excursion of the *Q-R-S* complex in any lead (Fig. 1). (3) Elimination of electrocardiograms with right axis deviation as *Q-3* is a normal finding in such records. (4) Exclusion of records with notching deformity of the *Q-R-S* complex in any lead, the so-called *W* and *M* complexes.

Clinical Correlation. The correlation of the electrocardiograms under discussion with the clinical diagnosis is given in Table 1. The greatest incidence of the characteristic electrocardiograms occurred in cases of hypertension, that is, of the 75 electrocardiograms with the large *Q-3*, 25 (33.3 per cent) were obtained in cases of this type. The anginal syndrome occurred only in 12 cases (16

per cent), luetic aortitis in 9 cases (12 per cent) and arteriosclerosis in 8 cases (10.5 per cent).

TABLE 1.—CORRELATION OF LARGE Q WAVES IN LEAD III WITH CLINICAL CONDITION IN 75 CASES.

Clinical diagnosis.	Cases.	Per cent.
Diseases affecting chiefly the left ventricle:		
Hypertensive heart disease	25	33.33
Anginal syndrome	12	16.00
Luetic aortitis	9	12.00
Arteriosclerosis	8	10.50
Total	54	72.00
Miscellaneous:		
Rheumatic heart disease	12	16.00
Postthyroidectomy	1	1.30
Cretinism	1	1.30
Auricular fibrillation (cause unknown)	1	1.30
Emphysema	1	1.30
Pregnancy (record after delivery did not show large Q-3)	1	1.30
Effort syndrome	1	1.30
Congenital heart	1	1.30
Apparently normal hearts	2	2.20
Total	21	28.00

Analysis of Results. Our results differ from those of Pardee,⁴ and those of Willius⁵ in some respects, but agree fairly well with those of the latter in the incidence of hypertensive heart disease (40 per cent). There is a discrepancy between the incidence of the anginal syndrome in our series (16 per cent) and that of Pardee (62 per cent) and that of Willius (25 per cent). However, the disagreement may be more apparent than real for the following reasons:

Angina pectoris is a symptom which varies with the "pain threshold" of the individual. This can very well account for the difference in the incidence of the anginal syndrome in groups of cases coming from different levels of society. There is certainly a great difference between the clientele of office practice and the type that is seen in a dispensary, where the incidence of luetic aortitis is high and the perception of pain is low.

Again, the difference in the interpretation of the anginal syndrome may be a factor; for the diagnosis of luetic aortitis very often takes in the symptom of precordial pain. Similarly, many a hypertensive case could be classified under the title of angina. But it is generally agreed that narrowing of the coronary, or of a branch, is the most frequent cause of the angina of effort; the pathologic changes underlying this syndrome are, however, admittedly various.

Therefore, we feel that the agreement between the total number or total percentage of cases having conditions that may give rise to coronary narrowing in each of the series of cases reported is just as important and as instructive as the agreement between the incidence of the anginal syndrome would be. Hence, if we add our

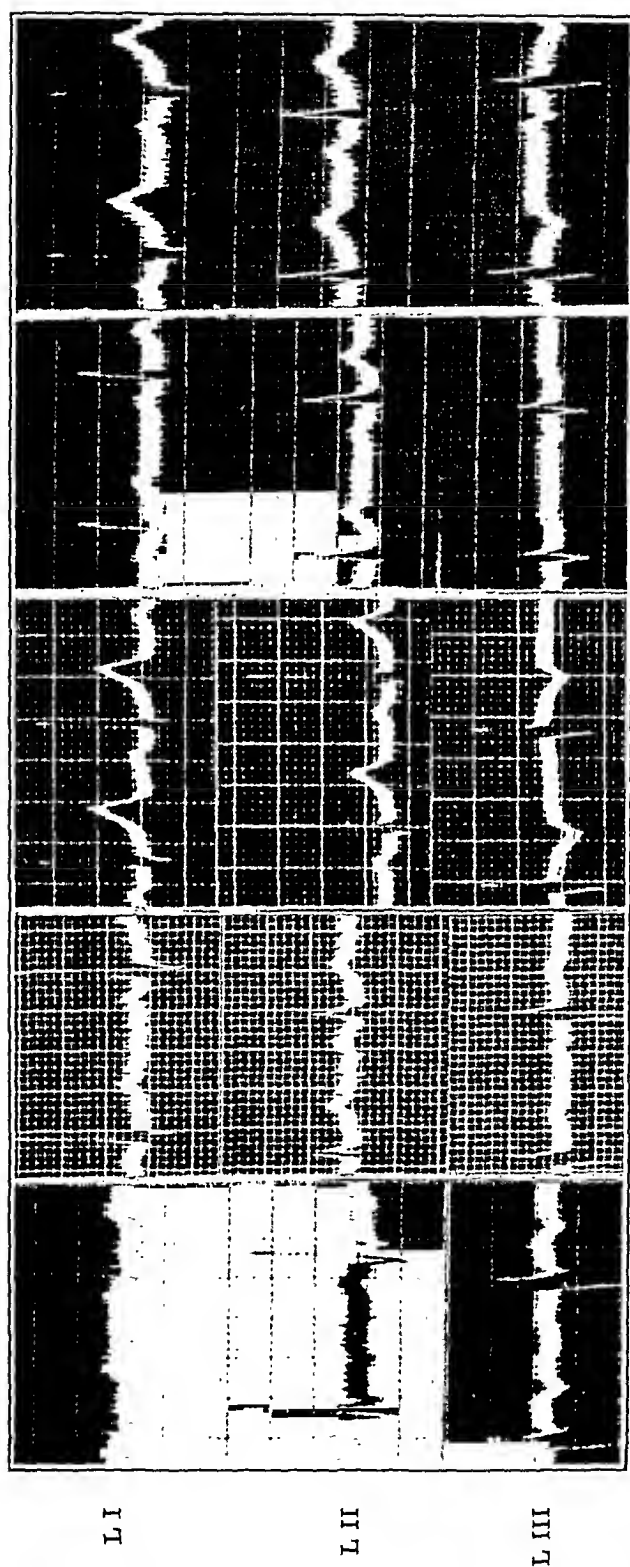


FIG. 1.—Large Q waves in Lead III of various types.

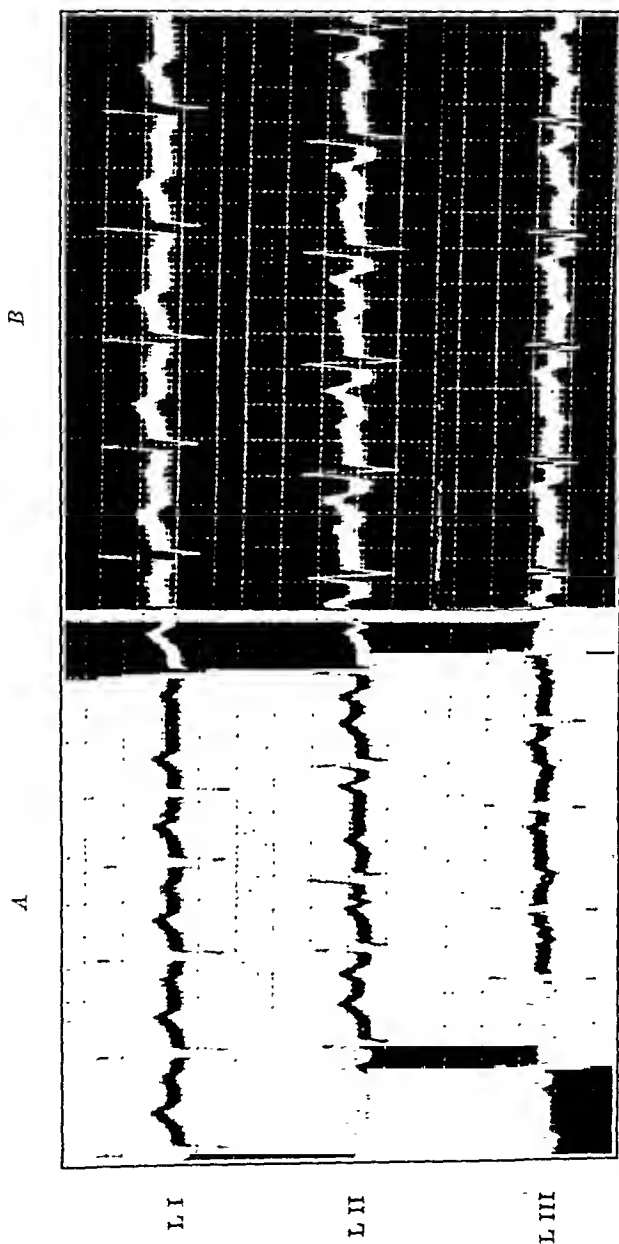


FIG. 2.—A, large Q wave in Lead III and auricular extrasystoles during pregnancy; B, disappearances of both abnormalities 1 year after delivery.

hypertensives, anginal syndrome cases, luetic aortitis and arteriosclerosis we get the sum of 54 cases out of 75 (72 per cent) that exhibit the large Q-3 (Table 1), as compared to Pardee's⁴ total of 81 per cent, and Willius's⁵ total of 89.8 per cent. Although these figures do not exactly agree, yet they are close enough to signify that this large Q-3 is evidently closely associated with pathologic changes that may involve the coronary arteries, or produce myocardial fibrosis.

The incidence of rheumatic hearts in our series with the large Q-3, 12 cases out of 75 (16 per cent) (Table 1), is entirely at variance with that of the other two series. Willius⁵ reports an incidence of 3 per cent and Pardee⁴ an incidence of 4 per cent. We wish to repeat that we excluded all cases of right axis deviation from this series. Pardee⁴ cites the work of Dr. Daniel Porte, who in a series of 23 cases of rheumatic heart disease with pericarditis found 6 cases (26 per cent) with the large Q-3. Pardee comments that there is something about the rheumatic invasion of the heart that gives rise to this abnormality in the electrocardiogram.

In this group of rheumatic hearts we have only 1 case of aortic stenosis, a patient, aged 59 years, and 1 case of mitral and aortic disease, in a child, aged 11 years. The rest showed involvement of the mitral valve alone. One was 3 years, 1 was 4 years, 2 were 10 years, 2 were 13 years, 1 was 46 years, 1 was 7 years of age, and the age of 2 was not recorded. The youngest children were in the active stage, having fever and tachycardia.

In analyzing the remaining 9 cases of the series with the large Q-3 wave we find varied conditions (Table 1), not unlike the miscellaneous group in the series of cases of Pardee⁴ and the cases reported by Willius.⁵ It is of interest to note, as in Pardee's series, we have a case of pregnancy with the large Q-3 wave that disappeared following the delivery. The auricular extrasystoles present during pregnancy also disappeared from the tracing following the delivery (Fig. 2). Pardee⁴ believes that the high position of the diaphragm favors the appearance of the large Q-3, while a low position is unfavorable.

Another interesting fact is the scarcity of normal hearts in this series of abnormal electrocardiograms. As mentioned previously, our files contained a number of tracings of normal hearts, and the incidence of apparently normal hearts in these 75 cases with large Q-3 wave is only 2 (2.6 per cent). One record is that of a student who has a high diaphragm and whose heart is of the hypersthenic type. In discussing the occasional occurrence of a large Q-3 in electrocardiograms of apparently normal hearts, Pardee⁴ suggested the possibility of an unusual distribution of the branches of the auriculoventricular bundle, as well as of a high diaphragm as contributory factors. The normals in Willius' series comprise 1 per cent while there were none in Pardee's series. The latter,⁴ in

reviewing the electrocardiograms of normal soldiers of the records of Dr. A. Cohn at the Rockefeller Institute, the electrocardiograms of normal hearts of patients of A. M. Masters of the Cornell Medical School, and the normal electrocardiograms of Lewis' series, found only 2 records with the large Q -3 waves in 277 tracings of normal hearts.

Associated Electrocardiographic Findings in Our Series of 75 Cases. Left axis deviation was present in 43 out of 75 cases having large Q -3 (57.3 per cent). The greatest incidence occurred about equally in the hypertensive group (76 per cent); in the anginal syndrome (75 per cent) and in the arteriosclerotic (75 per cent), while in the group with luetic aortitis there were only 44 per cent. In the rheumatic group (aortic and mitral) only 1 case in 16 (8.3 per cent) was seen with left axis deviation.

The direction of the T wave was normal in the majority of cases in this series (70 per cent). That is, they were upward in all leads or upward in Leads I and II and downward in Lead III. This compares well with Willius's figures of normal T waves (71.4 per cent), while Pardee's⁴ figures are somewhat lower (63 per cent). The incidence of significant T wave negativity in the various conditions is interesting as seen from the following figures: The arteriosclerotic showed significant T wave negativity in 50 per cent of their number; the luetic aortitis showed this feature in 44 per cent, the anginal group 41.6 per cent and the hypertensive 32 per cent; the rheumatic group showed none.

The occurrence of T wave negativity according to leads in our series varies greatly from that of Pardee.⁴ He states that the frequency of T_2 and T_3 inversion in his series to be 25 per cent as compared with T_1 and T_2 inversion of 11.5 per cent. In our series the ratio is reversed. T wave negativity in Leads II and III occurred only in 5.2 per cent while 21 per cent of our series displayed T wave negativity either in Lead I or in Leads I and II (Table 2). Our figures compare well with Willius' group, 19.6 per cent of cases displaying negative T_1 or T_1 and T_2 , and only 9 per cent displaying negative T_2 and T_3 . This ratio is in accord with the conception that there was strain predominantly on the left ventricle and conforms to the view of Barnes and Whitten⁷ regarding T wave negativity.

Pardee comes to the same conclusion, although T_2 and T_3 negativity predominates in his group. The latter finding together with the clockwise rotation of the vectors of the Q - R - S group in these tracings he considers as features depending on right ventricular activity. Hence, he concludes that the large Q -3 indicates disease of the left ventricle, so that the right ventricle predominates during the spread of the contraction in spite of the left axis deviation or normal axis direction of the Q - R - S .

In this group of 75 cases the only significant electrocardiographic

finding in 53 cases (70.7 per cent) was the large $Q-3$. Hence, it seems that the large $Q-3$ is a significant electrocardiographic feature, and when present without any other abnormality may be looked on as being an additional diagnostic sign. It appears to occur most often in diseases exerting their influence predominantly on the left ventricle, whether the anginal syndrome is present or not. The incidence of the rheumatic group in our series is the greatest so far reported. Either there is an actual damage to the left ventricular muscle as suggested by Pardee, or it may be due to the effect of a considerable septal displacement because of the hypertrophy, especially in advanced rheumatic hearts, as suggested by Fenichel and Kugel.⁶

TABLE 2.—ASSOCIATED SIGNIFICANT T WAVE NEGATIVITY.

	Cases.	Per cent.
Lead I	7	9.3
Leads I and II	9	12.0
Leads II and III	4	5.3
Leads I, II and III	2	2.6
Total	22	29.2

Summary. 1. Seventy-five cases with a large $Q-3$ wave are presented.

2. The majority of these records (54 cases, or 72 per cent) occurred in patients in whom there is apt to be involvement of the coronaries or their mouths, fibrosis of the myocardium, or cardiac hypertrophy with functional strain on the left ventricle.

3. Clinically these patients had one of the following conditions: Hypertensive heart disease (33 per cent), frank anginal syndrome (16 per cent), acute aortitis (12 per cent) and arteriosclerosis (10.5 per cent). All these diseases are known to exert their influence chiefly on the left ventricle.

4. The rheumatic heart group made up 16 per cent of the series—the highest incidence so far reported. More investigation is necessary for the corroboration and interpretation of this finding. The remaining 9 patients (12 per cent) had miscellaneous conditions, some of whom had diseases that exert their influence on the left ventricle.

5. Left axis deviation was encountered in 43 cases (57 per cent).

6. T wave negativity was seen only in 29 per cent of the cases, the negativity in T_1 and T_2 predominating (21 per cent).

7. One transient $Q-3$ wave was observed in a pregnant woman. In the tracing 1 year after delivery it was absent.

8. Of the entire group, only 2 apparently normal hearts displayed this abnormal $Q-3$ wave (2.7 per cent).

Conclusion. The result of our study of the large $Q-3$ wave in our series compares favorably with that of the other series of cases reported, both in regard to the type of condition in which this abnormality is found and to the scarcity of this finding in normal hearts.

This abnormality in the electrocardiogram may be considered an additional diagnostic sign. It is rarely found in normal hearts and is usually associated with diseases that exert their influence chiefly on the left ventricle.

NOTE.—We wish to thank Miss Dorothy Sherman, the electrocardiographist at the Research Hospital, for her technical assistance in the preparation of this paper.

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GAUCHER'S DISEASE: REPORT OF 2 CASES, WITH A REMISSION IN 1 FOLLOWING ADMINISTRATION OF LIVER EXTRACT.

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GAUCHER'S disease, first described by that author,⁸ in 1882, as "primary idiopathic hypertrophy of the spleen," is a relatively rare constitutional disturbance. We report below 2 cases seen in the University Hospital, 1 successfully treated by splenectomy and 1 with a remission now lasting over a year, following our administration of liver extract. We have been unable to find in the literature any instance of a similar remission either in the symptoms or by diminution in the size of the spleen, the only palliative measure mentioned being splenectomy which is not regarded as influencing the eventual course of the disease.

Incidence. The literature pertaining to Gaucher's disease includes several summaries^{6,9} of all authentic cases reported. The other cases^{1,4,10,13,19} which do not appear in these tabulations, together with the 2 cases seen by us, brings the total number to over 100 reported instances of the disease.

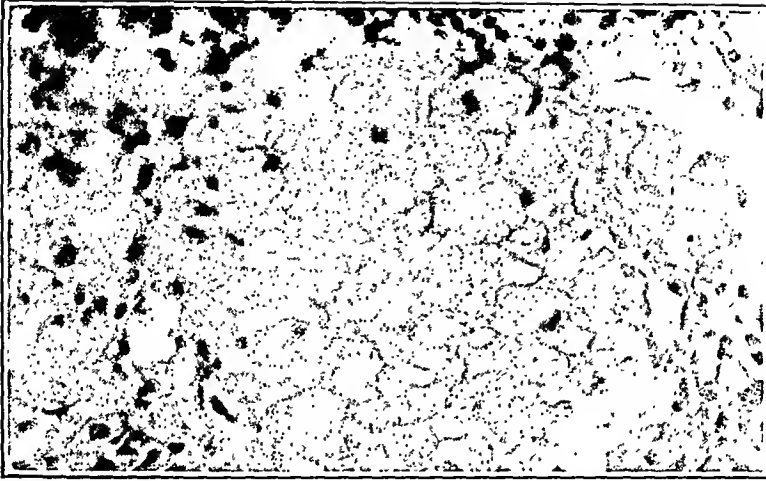


FIG. 1.—Case 1. Section of spleen, showing large Gaucher cells in reticulum of spleen.

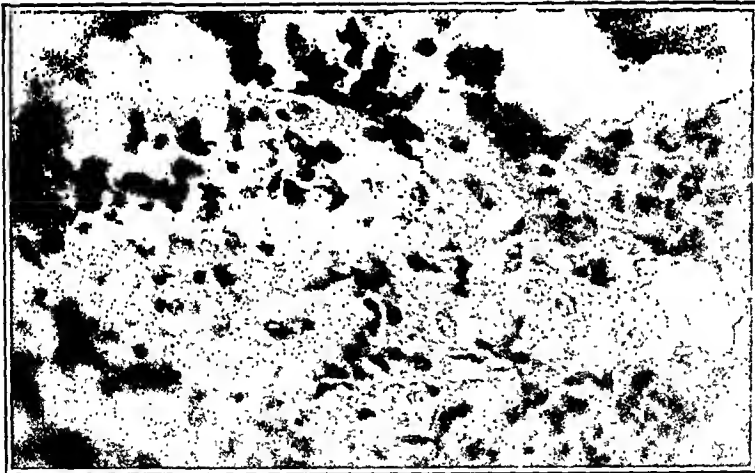


FIG. 2.—Case 2. Section of bone marrow with replacement of normal constituents by large closely packed cells characteristic of Gaucher's disease.

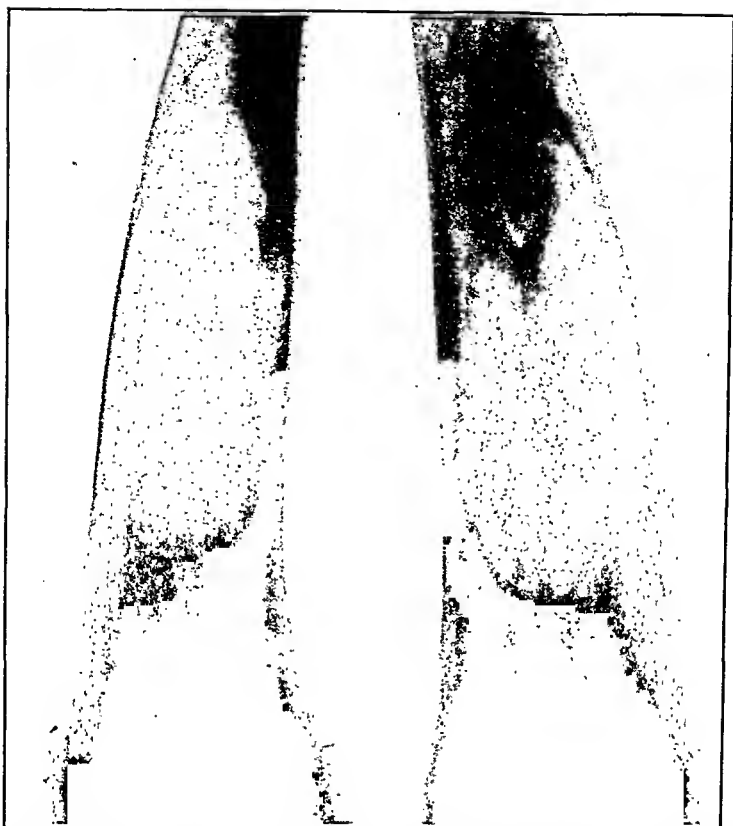


FIG. 3.—Case 2. Roentgen rays of right femur which show the diffuse expansion of the lower end of the femur. Note the mottled oval-shaped areas of decreased density with marked thinning of the cortex and absence of periosteal reaction.

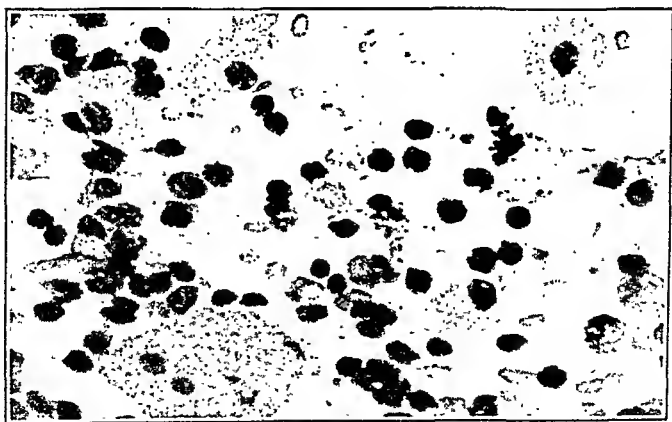


FIG. 4.—Case 2. Material from splenic puncture (dry film Wright's stain). Several Gaucher cells are seen in the preparation illustrating their comparative size and the character of the cytoplasm.

Pathology and Clinical Findings. The most recent complete information regarding Gaucher's disease has been written by Rowland,¹⁸ who has made an exhaustive study of the diseases of lipid metabolism, and who has seen perhaps more cases of Gaucher's disease than anyone in this country today.*

Gaucher's disease is regarded as a disturbance of the lipid metabolism with the production and accumulation of a complex lipid known as kersasin, the biochemical nature of which was established by Epstein.⁷ This work has been confirmed by Cushing and Stout,⁶ Bloom and Kern³ and Beumer.²

The clinical picture of the disease is often quite clear and the diagnosis readily made. The course of the malady is chronic, with an insidious course in early life and often extending over a long period of years. Death from the disease itself is uncommon, usually being due to anemia and intercurrent infections.

Bone Changes. Gross skeletal changes in Gaucher's disease, pointed out by Pick,¹⁷ in 1922, have excited interest following the radiographic observations of Klercker¹⁴ and Junghagen,¹² in 1926. In some instances the bone lesions have been a predominate manifestation of the disease which has led to the diagnosis, since the radiographic studies are characteristic. The changes usually seen are: (1) Thickening of the shafts of long bones; (2) localized swellings over bones; (3) pathologic fracture. The patient may complain of pain and tenderness over the involved bone, or of difficulty on joint motion. Pain, swelling, redness and exquisite tenderness to palpation may occur over a bone to a degree that the condition simulates osteomyelitis and operation may even be done for that diagnosis. This occurred in 1 of the cases seen by us (Case 2) and has also been reported by Moschcowitz¹⁶ and by Welt.¹⁹

Case Reports. CASE 1.—L. M. (No. 162212), female, aged 12 years, colored, was admitted to the University Hospital, February 10, 1927, with an abdominal tumor which had been present 2 years with a gradually increasing size. Increasing pallor had been noted for 1 year, and frequent epistaxes for 2 years. The past history was unimportant. There was no history of a similar illness in the family.

Physical examination showed an underdeveloped and undernourished negress. There was nothing unusual about the skin or eyes. The spleen was greatly enlarged, extending 2 inches to the right of, and 2 inches below the umbilicus. The liver extended 3 fingerbreadths below the rib margin. The peripheral lymph glands were not enlarged.

Blood studies: The hemoglobin was 60 per cent (Sahli); red blood cells, 3,320,000; white blood cells, 5900; differential count was normal. The platelets were 150,000. The blood chemistry was entirely normal, including the blood sugar, nonprotein nitrogen, blood chlorid, blood cholesterol, serum protein, albumin and globulin and the erythrocyte fragility test.

Biopsy of the lymph glands and of rib bone marrow were normal. A pre-operative diagnosis of Gaucher's disease was made, and on June 13, 1927,

* See also the 1932 Dunham Lectures by Prof. Ludwig Pick, shortly to appear in this Journal. (EDITORS.)

the spleen was removed. *At operation* the spleen was greatly enlarged and had many adhesions, but on gross examination was not unusual.

Histological examination (Dr. C. V. Weller): "The spleen is characterized by an extraordinary hyperplasia and hypertrophy of the reticulo-endothelial cells lining the greatly dilated blood sinuses. The lymph follicles are preserved and there is no evidence of a leukemia or other lymphoblastomatous condition. Frozen sections show the large cells lining the sinuses to be free from complex stainable lipoids. The spleen, therefore, falls into the more restricted type of Gaucher's disease in contrast to the type with stainable lipoids which is now called Niemann's disease" (Fig. 1). Stains for iron were not done.

The patient improved rapidly following this operation and was discharged in 6 weeks with the hemoglobin 72 per cent and red cell count 4,800,000.

CASE 2.—A. U. (No. 262321), male, aged 17 years, Austrian (parents), was admitted to the University Hospital, April 7, 1931, complaining of severe pain of 3 days' duration in the lower third of the right thigh. For 11 years he had had recurrent attacks of pain in the long bones of the lower extremities and 7 operations had been done upon the bones of the legs. Healing had occurred in from 3 weeks' to 1 year's time.

Past history: Frequent severe epistaxes had occurred at intervals for several years.

Family history: Seven brothers living and well, with no affection similar to that of the patient, and 2 brothers dead, cause unknown. No familial diseases known.

Physical examination showed a boy of the stated age with a normal physical and mental development. *Skin* was sallow, with a brownish pigmentation over the cheeks and temples. The mucous membranes were pale and colorless. *Eyes* showed wedge-shaped translucent plaques of yellow fat on the nasal sides of the conjunctivæ, the bases of the wedges being toward the irides. *Liver* was felt 3 fingerbreadths below the right costal margin. *Spleen* was felt 2 fingerbreadths below the left costal margin in the anterior axillary line and extended to the right past the left midclavicular line. The edge was smooth and the notch could be felt. *Extremities:* Healed incisions were present on the right thigh and over the right and left legs. The lower third of the right femur was thickened and exquisite tenderness was elicited on pressure. *Lymph glands* of the peripheral group were normal. The temperature was 101° F.; hemoglobin, 50 per cent (Sahli); red blood cells, 3,900,000; white blood cells, 8000. Urine and blood Kahn were negative.

Roentgen ray films (Fig. 3) showed a symmetrical enlargement of the lower half of the right femur with a thin cortex and a large oval area of decreased density just above the condyles. A small irregular area of increased density in the middle of the shaft suggested sequestration, and a diagnosis of chronic osteomyelitis was made.

Clinical course: The right femur was explored through a lateral incision the day of admission. There was edema over the periosteum and through a window in the cortex, the medulla was found filled with a chocolate-colored gelatinous material which gave no bacterial growth on culture. A small sequestrum was removed. Microscopic examination of the tissue removed showed no inflammatory reaction, the bone marrow being replaced by large xanthomatous foam cells resembling those of Gaucher's disease (Fig. 2).

Complete studies were then made on the blood and showed normal blood nonprotein nitrogen, calcium, phosphorus, cholesterol and bilirubin. The bleeding and clotting time, erythrocyte fragility and glucose tolerance tests were normal.

Roentgen ray films of all the long bones were then made and showed involvement of the left femur and both tibiæ by a lesion similar to that seen in the right femur.

The patient was repeatedly transfused, with no improvement. In April, 1931, on the advice of Dr. R. Isaacs, the patient was given liver extract (Lilly), 4 vials daily. Many red blood cells were oval and in measuring them (stained) 12 per cent were smaller than 7.5 micra and 23 per cent larger. The tendency to large oval forms suggested the possibility that liver extract would have a somewhat similar action on the bone marrow to that in pernicious anemia, where oval macrocytes are characteristic.

Except for short periods, he has continued to take 3 to 4 vials daily up to the present time, a period of 11 months. There has been during this period a progressive improvement and at present the patient looks and feels better than he has for many years. The pigmentation over the face has disappeared and the plaques on the eyes are much less noticeable. Epistaxes are very infrequent. There has been a decrease in the size of the spleen and to a lesser degree of the liver. The blood (March 3, 1932) shows the hemoglobin, 66 per cent (Sahli); red blood cells, 4,500,000; white blood cells, 7800. The differential smear and platelets are normal.

Histologic examination (Dr. C. V. Weller) of material obtained by splenic puncture (Fig. 4): "Scattered through the large amount of blood there are huge mononucleate and binucleate endothelial cells with a finely vacuolated cytoplasmic reticulum. Since the contents of these vacuoles do not give positive results with the ordinary fat dyes this corresponds to Gaucher's disease." Stains for iron were not done.

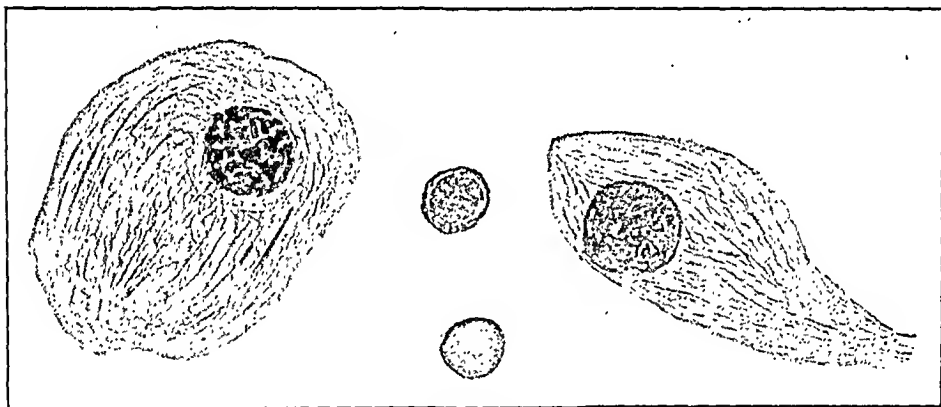


FIG. 5.—Case 2. Cells from splenic puncture material (dry film Wright's stain). The fibrillar character of the cytoplasm is shown. A red blood cell and a small lymphocyte are shown to indicate the relative size. (Drawn by Dr. R. Isaacs.)

Comment. Case 1 who had spleneectomy has never returned to the clinic and we have been unable to trace her since making this study.

In Case 2 operation was done before the correct diagnosis had been made, but microscopic examination of the tissue removed at operation and later by splenic puncture proved the diagnosis. The anemia which was present was of major importance, since, as is the rule in Gaucher's disease, transfusions were of no help, the blood picture, in fact, being lower following 2 transfusions than it was previously.

The use of liver extract was suggested on a purely empirical basis. It was felt that since this substance was of proven value in the treatment of primary anemias, as well as in some other

varieties,¹¹ it might prove helpful in Gaucher's disease for which, to our present knowledge, there is no cure. Splenectomy, which has a favorable influence upon the hemorrhagic diathesis in about 50 per cent of cases, has no effect upon the disease itself, and carries an operative mortality of 25 per cent.

Although we earnestly wish to disclaim the idea of a cure for Gaucher's disease by the use of liver extract, it seems probable that the remission of both subjective and objective findings during the administration of liver extract is more than coincidence. This appears especially tenable since all published reports of the disease characterize it as progressive and not subject to remissions.

Reduction in size of the spleen has not been previously reported in connection with Gaucher's disease, and even though careful measurements, checked by several examiners, had failed to show actual diminution in its size, a Gaucher spleen remaining the same size for a year would be unusual.

In regard to the manner in which liver extract may have acted in this case, we are unprepared to venture any theory, but offer the suggestion that the procedure may be of some value in the future treatment of this disease.

Summary. 1. Two proven cases of Gaucher's disease are added to the reported cases which now total over 100.

2. The first case was improved immediately following splenectomy, but no recent checkup has been possible.

3. The second case had bone lesions mistaken for osteomyelitis and operation was done for this diagnosis.

4. This case was then given liver extract (Lilly) over an 11-month period with the occurrence of a remission characterized by symptomatic improvement, diminution in the size of the spleen and liver and improvement in the blood picture.

5. Although lacking any knowledge of the *modus operandi*, liver extract is suggested in the treatment of Gaucher's disease.

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UNDULANT FEVER.*

SOURCES, MODES OF INFECTION, AND PROPHYLAXIS.

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STUDIES of undulant fever in the United States have been in progress for only the last 5 years, but in this short interval much has been learned concerning the disease in man and the source of the infection. The evidence thus far accumulated indicates that domestic animals, principally cattle and swine, are the chief hosts of *Brucella abortus*, and transmit the infection to the human family through dairy products and by contact. The methods leading to the control and ultimate eradication of infectious abortion in animals and the prevention of undulant fever are, comparatively speaking, simple, but from a practical standpoint are difficult. The chief difficulties, we believe, are a lack of information on the part of the animal owner, and the great economic factor involved.

The incidence of *Brucella abortus* infection in cattle in the United States has been found to be from 15 to 20 per cent, while in swine we¹ observed 1.5 to 2 per cent of about 4000 samples of blood to show *abortus* antibodies. In this country no data are available on animals such as sheep, goats, birds, etc., but basing our judgment on published reports, we consider that the disease in these species is relatively uncommon and that, in general, the danger to man is negligible. An exception to this statement, however, is the *Brucella melitensis* infection in goats of the southwestern states. We wish to emphasize that any species of animal infected with the genus *brucella* is a potential danger to man.

Many of those engaged in the animal industry are not aware of the extent of *Brucella abortus* infection in animals, and do not appreciate that many seemingly normal animals are carriers of the organism and will spread the disease to susceptible animals. If an animal aborts it seldom shows other clinical signs of disease unless secondary infection takes place. The great natural resistance of swine and cattle, and also the frequently acquired immunity to

* This work was made possible by a research grant from the Metropolitan Life Insurance Company. Part of this work was done in the Department of Pathology, Albany Medical College, Albany, N. Y.

the causative agent, have resulted in underestimating the economic losses to the live stock industry and the hazard to the human family.

In 1924, when the attention of bacteriologists in this country was attracted by Keefer's² report that *Brucella abortus* had been isolated from the blood of a patient who had suffered from a continuous fever of several weeks' duration, we had access only to the information on Malta fever, made available by the English Mediterranean Fever Commission. At present we have many data on the incidence and course of the disease in man and animals, modes of infection, dissemination of the virus and some information concerning the pathology of the disease. Although we can be certain that *Brucella abortus* is the infective agent, we need more data on methods for identifying those strains pathogenic for man. The treatment of the disease is still far from being satisfactory. During the last four years many laboratories have begun studies on some phase of *Brucella abortus* infection, and nearly all of the larger laboratories engaged in routine work are prepared to make examinations for evidence of disease due to this organism. There are now more than 100 cases of undulant fever diagnosed each month in the United States.

The prevention of any disease demands a knowledge of the source of the virus, how the virus gains entrance to the body, and how an individual may be immunized to that virus if the tissues are invaded. We have considerable information concerning the first two factors in undulant fever, but only a few data on immunity to this infection.

Man may become infected either by consuming dairy products containing *Brucella abortus* or by wound infection. In this report it seems unnecessary to submit all the data that have been published concerning sources of infection. After the organism has gained entrance to the digestive tract, it invades the normal or diseased mucous membrane, thereby passing into the blood stream directly or indirectly by way of the lymphatic system. The lymphatic and blood stream may become invaded more directly by infection from the tonsils. Experimental work³ on feeding calves *Brucella abortus* in milk showed that the lymph nodes draining the mouth and the pharynx became invaded first and harbored the organism longer after the infective milk had been withheld than any other tissues in the body. Several investigators have isolated *Brucella abortus* from human tonsils after surgical removal. In our own series we observed the organism in 8 of 56 pairs.²³

Although we know of no instance in which *Brucella abortus* has been isolated directly from a wound in man, it is evident that undulant fever may result from the infection gaining access to the tissues through a wound. It seems unlikely that the invasiveness of *Brucella abortus* is great enough to permit it to penetrate the unbroken human skin, although there is evidence to show that this

is possible in guinea pigs. Hardy, Hudson and Jordan⁴ reported infection of guinea pigs when cultures of *Brucella abortus* were placed on the unabraded skin. They observed that, in general, porcine strains were more invasive for the skin of the guinea pig, while bovine strains caused a higher percentage of infections when introduced into the digestive tract.

TABLE 1.—RESULTS OF FEEDING CULTURES OF *BRUCELLA ABORTUS* TO GUINEA PIGS.*

Bovine.					Porcine.				
Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.	Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.
802	12,000,000,000	+	+	+	781	12,000,000,000	+	+	+
801	3,000,000,000	+	+	+	780	3,000,000,000	+	+	+
800	750,000,000	+	+	+	779	750,000,000	+	+	+
799	187,500,000	—	—	—	778	187,500,000	+	+	+
798	46,875,000	+	+	+	810	46,875,000	+	+	+
797†	11,718,750	+	+	+	811	11,718,750	—	—	—

* The series of multiple dilutions were made by diluting a 12,000,000,000 suspension with equal parts of a sterile physiologic salt solution, discarding every other dilution.

† 9 animals in each series given increasingly weaker suspensions were negative to all 3 tests.

TABLE 2.—RESULTS OF PLACING CULTURES OF *BRUCELLA ABORTUS* ON UNABRADED SKIN OF GUINEA PIGS.*

Bovine.					Porcine.				
Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.	Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.
754	12,000,000,000	+	+	+	796	12,000,000,000	+	+	+
750	3,000,000,000	+	+	+	795	3,000,000,000	+	+	+
753	750,000,000	+	+	+	776	750,000,000	+	+	+
770	187,500,000	+	+	+	777	187,500,000	+	+	+
755	46,875,000	+	+	+	774	46,875,000	+	+	+
751	11,718,750	—	—	—	775	11,718,750	—	+	Slight
752	2,929,687	—	—	—	759	2,929,687	—	—	—
771	732,421	—	—	—	745	732,421	+	+	+
793†	183,105	—	—	—	772	183,105	—	—	—

* The series of multiple dilutions were made by diluting a 12,000,000,000 suspension with equal parts of a sterile physiologic salt solution, discarding every other dilution.

† 7 animals in each series given increasingly weaker suspensions were negative to all 3 tests.

We have recently completed a similar experiment to determine whether guinea pigs are more readily infected with *Brucella abortus*

by feeding or by skin inoculation. Porcine and bovine strains were used in these studies, and although we observed very little difference between the invasiveness of the two strains for guinea pigs, our data are in accord with those of Hardy and his collaborators. (Tables 1 and 2.)

After it had been determined that guinea pigs can be readily infected by placing bovine and porcine strains of *Brucella abortus* on the unabraded skin, we desired to find out what effect the application of disinfectants would have on these areas after inoculation. One-tenth cubic centimeter of a suspension containing 12,000,000,000 organisms per cubic centimeter was placed on the skin and spread over the area with a quartz spatula. The area of skin used was about 1 cm. in diameter and located posterior to the base of the ear. This area is very satisfactory because it is devoid of hair, hence requiring no treatment before applying the culture. This area is also difficult for the guinea pig to scratch with his feet and thus contaminate his food and infect the digestive tract. Two guinea pigs were used for each inoculation, which were kept in individual cages. Ten minutes, 30 minutes and 4 hours after the culture had been placed on the skin of each group applications of the following disinfectants were made over the areas inoculated: 5 per cent solution lysol, 1 to 1000 aqueous solution bichlorid of mercury and 70 per cent alcohol. The inoculated area of a fourth group was washed with a 12 per cent solution of ivory soap and water. The guinea pigs were autopsied from 4 to 5 weeks later and examined for evidence of *Brucella abortus* infection. The results were striking because, in practically every instance (Table 3) infection followed the inoculation, regardless of the application of disinfectants. At present we are continuing this experiment to determine whether other disinfectants are more efficient, and just how rapidly the microorganisms pass through the normal skin of the guinea pig. The results obtained from the studies on guinea pigs are only indicative of what may occur in the human. The integument of man is much thicker than that of the guinea pig, and doubtless the resistance to extraneous infection is thereby proportional.

TABLE 3.—NEGATIVE RESULTS OF APPLYING DISINFECTANTS TO SKIN OF GUINEA PIGS UPON WHICH CULTURES OF *BRUCELLA ABORTUS* HAD BEEN PLACED.

Disinfectant.	10 minutes.		Time, 30 minutes.		4 hours.	
	B	P	B	P	B	P
Bichlorid of mercury, 1 to 1000	+	+	+	+	+	+
Lysol, 5 per cent	+	+	+	+	+	+
Ivory soap and water	+	+	+	+	+	+
Alcohol, 70 per cent	+	+	+	+	+	+

B, bovine; P, porcine.

2 guinea pigs used for each disinfectant and each interval.—Total of 48.

It is evident that man may become infected with *Brucella abortus* from an invasion of the normal conjunctiva with or without the

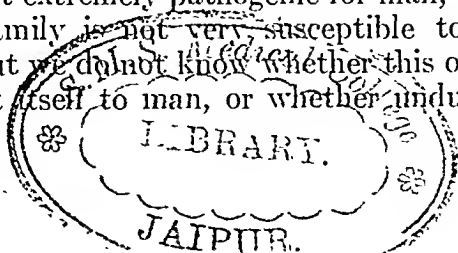
development of lesions of the eye. An infective exudate could spatter into the eye, or be introduced by a finger contaminated with the organism. A laboratory worker, especially, is exposed to such hazards. Schroeder and Cotton⁵ demonstrated experimentally that they could infect guinea pigs with the bovine and porcine strains of *Brucella abortus* by introducing into the eye 1 drop of a saline suspension of the organism. Only one-third of the animals receiving the bovine strain showed lesions of abortion disease at autopsy, while all of those inoculated with the porcine strain became infected. In only 1 case was the eye observed to be diseased grossly. Later they⁶ inoculated a heifer by placing 1 drop of a *Brucella abortus* suspension in one eye. The animal became infected and aborted in 54 days.

Orloff⁷ has recently reported 2 patients with undulant fever, who showed extensive lesions of the eye during the course of the disease. He also described lesions observed in the eyes of 19 guinea pigs experimentally infected with *Brucella abortus*. He observed a parenchymatous keratitis, iritis, iridocyclitis, choroiditis, neuroretinitis and an inflammatory cataract. He states that the lesions produced by *Brucella abortus* are very similar to those resulting from tubercle bacillus infection of the eye, and no doubt many cases of the former are erroneously diagnosed. Such information emphasizes the fact that when handling tissues or suspensions containing *Brucella abortus* precaution must be taken to avoid eye infection.

We believe that there are three groups of individuals who are exposed to infection with *Brucella abortus* and *Brucella melitensis*: (1) Consumers of dairy products; (2) animal husbandrymen and the handlers of fresh meats; (3) veterinarians and laboratory workers engaged in research on infectious abortion, or in the routine examination of material for evidence of abortus infection. This grouping is purely arbitrary because those composing the second and third groups may likewise be classed with Group 1 when they are exposed to the infection from drinking raw milk. But in as much as the methods of prevention of the infection in each instance are so different this classification serves our purpose well.

We could simplify this report by stating that the eradication of infectious abortion in domestic animals would prevent undulant fever in man. This is the ultimate goal of those engaged in the control of abortion disease. However, from our knowledge of infectious disease, we realize that unless a cure for this malady is discovered, the elimination of the disease by the Bang method will require a half century or perhaps longer, and many cases of undulant fever will occur in the meantime.

Brucella abortus is not extremely pathogenic for man, or we may say that the human family is not very susceptible to infection with this organism. But we do not know whether this organism is just beginning to adapt itself to man, or whether undulant fever



has not been recognized in the United States until recently. In our opinion, both factors have been operating, but because of this recent knowledge that there is danger to man, greater control measures will be taken to prevent further spread of the disease in animals.

The examination of a comparatively large number of human blood samples from various states shows that from 5 to 7 per cent of those individuals living in the country or in small towns, or cities where most of the milk sold is not pasteurized, carry abortus antibodies in their blood. This indicates that many no doubt have developed an active immunity to the infection. This may be the result of a mild infection unrecognized, a case of undulant fever diagnosed as due to some other infection or due, perhaps, to the ingestion of living organisms without causing symptoms of disease.

The first group, the consumers of dairy products, are exposed chiefly by drinking raw milk or cream containing the infective agent. Pasteurization of milk from cows infected with *Brucella abortus* will protect this group. Arnold⁸ reports that it requires a temperature of 140° F. for 40 minutes to destroy the porcine type of *Brucella abortus*, and that the temperature and length of time at which milk is ordinarily pasteurized, *i. e.*, 140° to 145° F. for 30 minutes, will not kill the most pathogenic strains of *Brucella abortus*. Yet the abundance of evidence indicates that pasteurization does destroy *Brucella abortus*.

In 1928 we⁹ reported our findings concerning the effect of temperatures of 140°, 142° and 145° F. on cultures. A total of 8 cultures were studied, 4 bovine, isolated from milk, 3 human and 1 porcine. The porcine culture was more resistant than most of the human and bovine strains. It required 20 minutes at 140° F., 15 minutes at 142° F. and 10 minutes at 145° F. to render it non-viable. One bovine and 1 human strain were as resistant to the process as the porcine type. The remaining strains examined were not viable after 15 minutes at 140° F., 10 minutes at 142° F. and 5 minutes at 145° F. Recently we¹⁰ determined the thermal death time of 10 extremely virulent so-called porcine strains of *Brucella abortus* isolated from swine and man. Heating the cultures in milk for 30 minutes at 142° F. killed all of the organisms, demonstrating again that our present requirements for the holding method of pasteurizing milk are adequate to kill *Brucella abortus*. MacFadyen and Stockman,¹¹ of England, Zwick and Wedeman,¹² of Germany, and Park¹³ have likewise reported that *Brucella abortus* is destroyed by these temperatures.

We have studied this problem from three different standpoints: (1) The thermal death time of human, bovine and porcine cultures of *Brucella abortus*; (2) the examination of 205 samples of pasteurized milk and cream from 50 cities and towns in 5 states for evidence of the infection; (3) the incidence of undulant fever in communities

before and after ordinances were passed requiring raw milk to be pasteurized or to be free from *Brucella abortus*.

TABLE 4.—EXAMINATION OF PASTEURIZED SAMPLES OF MILK AND CREAM FOR *BRUCELLA ABORTUS*.

State.	Number of cities and towns.	Number of samples of milk and cream.	Results of guinea pig injection.
New York	39	152	Negative.
Massachusetts	7	18	Negative.
New Jersey	2	2	Negative.
Illinois	1	20	Negative.
Indiana	1	13	Negative.
Total	50	205	

Table 4 shows the results of examining 205 samples of pasteurized milk and cream collected from 50 small towns and cities in 5 states. The majority came from New York State, but through the courtesy of Dr. Arnold Kegel, of the Department of Health, Chicago, 20 samples were obtained from Chicago for examination, while Dr. A. S. Giordano shipped us 13 samples from South Bend, Ind. Eighteen samples were collected from the western half of Massachusetts and 2 from New Jersey. The samples were collected from pasteurizing plants, distributing stations, stores and restaurants, packed in ice and taken to the laboratory as soon as possible. The cream was allowed to rise on each sample of milk, after which 2 cc. of the cream were injected subcutaneously into guinea pigs. The same amount of pasteurized bottled cream samples was also injected into the guinea pigs. The guinea pigs were examined for evidence of *Brucella abortus* infection, approximately 4 weeks after injection. The tissues were inspected for lesions, and cultures were made from the spleen and incubated at 37.5° C. in an atmosphere containing 10 per cent carbon dioxide. *Brucella abortus* was not recovered from any of the 205 samples examined. Agglutination tests made on the guinea pig serums were likewise negative. When one considers the many different types of pasteurization equipment used, and the varying conditions under which these samples were pasteurized, we feel that this is another general indication of the efficiency and value of the process. Carpenter and King¹⁴ have reported that 20.4 per cent of the raw milk supply of three counties in central New York showed *Brucella abortus* infection. Evans,¹⁵ Fleischner and Meyer,¹⁶ as well as others, have reported similar findings. Therefore, it is probable that approximately 40 of the 205 samples tested contained *Brucella abortus* before pasteurization. The temperatures at which these samples were pasteurized varied from 142° to 145° F. for 30 minutes. We have no information on the pathogenicity of the strains of *Brucella abortus* in the milk nor on the number of organisms present prior to the pasteurization. There have been isolations from milk

samples very virulent strains of *Brucella abortus* that have been classified by some investigators as porcine types. Therefore, we cannot assume that all were of low virulence and that none would have infected man.

The epidemiology of undulant fever is interesting in that very few cases have occurred in communities where the milk is pasteurized. On the other hand, instances have been recorded of the occurrence of a series of cases on a raw milk route, or in a community where the milk is not pasteurized. As a rule, not more than 1 case of the infection occurs in a family, even though all the members of the family may be drinking the same milk. In those communities where undulant fever has been reported and later ordinances have been passed by the local boards of health requiring either pasteurization of the milk or the elimination of those animals discharging *Brucella abortus* in their milk rarely have more cases of the disease been diagnosed. A typical example of this may be cited from data obtained from the Board of Health at Ithaca, N. Y., where this work was begun. In $2\frac{1}{2}$ years 17 cases of undulant fever were diagnosed. During this period efforts were made to locate and eliminate the source of the infection. As soon as pasteurization was encouraged, many of the smaller distributors sold their milk to larger dairies, who pasteurized the milk. At present all the milk is pasteurized except that from one dairy that produces a raw milk for babies, and the owner of this herd has eliminated the infected animals. With the exception of a university student who spent the summer months out of the city, no cases of undulant fever have been reported during the past 2 years. Similar evidence has been submitted by Farbar and Mathews¹⁷ on an epidemic of undulant fever with a study of the milk supplied to this community. Studies of patients at the Metropolitan Life Insurance Company Sanitarium¹⁸ before and after *Brucella abortus* was eliminated from their milk supply demonstrate the value of pasteurization.

Although one occasionally obtains a history from a patient with undulant fever, stating that only pasteurized milk has been drunk, we find in most instances, after careful questioning, that unpasteurized cream has been used on cereals or other uncooked foods. The history of a patient who states that he is not a so-called "milk drinker" often reveals this same information. Patients also forget until questioned that they were on vacations, the guests of friends, or attended social gatherings where the quality of the milk or cream was unknown.

Because many cases of undulant fever occur in the country districts and on farms, where raw milk is consumed and there are no facilities for pasteurizing milk except by boiling, an entirely different problem is presented. The dairy husbandrymen not only suffer the great economic loss from infectious abortion but are also exposed to hazard of contact infection. Pasteurization of milk

does not protect those men engaged in abattoirs, men who slaughter animals, cut, handle and inspect raw meats. Many of these individuals do develop undoubtedly an active immunity, while others, for reasons still undetermined, are susceptible and are incapacitated for long intervals with undulant fever.

To protect this group from the disease, we must either eliminate the infection from our livestock which is the source of the disease for man, prevent infection from occurring through wounds, or immunize man to the infection. At present we do not have satisfactory information to determine whether the latter procedure can be successfully accomplished. The education of the dairyman and those engaged in abattoirs to the dangers of handling infected animals or tissues where wounds are present on the hands or arms is important. Immediate disinfection of wounds, inflicted while working with possibly infected material, is necessary. The use of rubber gloves, or some other protection, when abrasions or open wounds are present, would prevent many cases of undulant fever, especially among abattoir workers. Nevertheless, the eradication of infectious abortion from the livestock industry is urgent. Control methods are well understood by veterinarians and by many laymen. Fourteen states and the territory of Hawaii have already passed laws prohibiting the admission of cattle infected with *Brucella abortus*. The Federal government, as well as the majority of the state bureaus of animal industry, is actively engaged in research to prevent the further spread of infectious abortion, or is employing control measures.

The method of control is relatively simple. Specific treatment has failed, but the detection of infected animals, followed by their elimination or isolation has proven to be a most satisfactory plan for establishing herds free from the disease. The agglutination test, or "blood test" as it is commonly called, is not 100 per cent efficient and has certain limitations, but it will nearly always determine the infected animals in a herd. Occasionally an animal infected with *Brucella abortus* will not show antibodies in its blood serum. There are instances where the serum from an infected cow will not agglutinate the *abortus* antigen for a few days prior to, or following an abortion or parturition. However, it is as efficient as the Widal test for typhoid in man, and is the most important aid in the control of infectious abortion in domestic animals. The blood test requires a well-trained serologist and the interpretation of the results of the test should be made by one who understands the clinical phases of the disease and at the same time has a knowledge of the blood test and its limitations.

The infected animals should be eliminated from the herd or segregated. Because of the economic factor, many dairymen cannot always sell or slaughter the infected cows that may be producing well. In that case, isolation of the infected cattle from the normal

animals may be carried out. If two stables are not available, a temporary partition may be installed to separate the two groups, and with intelligent care a herd free from the disease can be established. Every effort should be made to test the blood of range cattle and to keep the positive reactors from the negative group. The experience gained in the eradication of bovine tuberculosis in animals has proven of great value to those agencies interested in the eradication of infectious abortion. This problem is much simpler than that of bovine tuberculosis because cattle may be tested as often as desired. Furthermore, calves may nurse infected dams with impunity. A higher percentage of cows, though small, recover from the disease than from tuberculosis.

Even though an animal owner is not in a position to dispose of his infected animals or to isolate them, we believe that the blood test is still valuable. The results are an asset to him by showing the status of his herd. With the knowledge that a cow is infected, he may watch her for premonitory symptoms of abortion and isolate her from the herd. This protects uninfected animals from the greatest danger, because the placenta and uterine exudate are the most infectious material and massive doses of the organism are present to spread the disease. The milk from such an animal should not be used for home consumption unless pasteurized. We have studied 2 cases of undulant fever in each of which the milk from the only infected cow in the herd was saved for family use. The animal owner can protect himself or those in his employ by not removing the placenta if it be retained, as usually occurs following late abortions. He should refrain from this, especially if there are wounds on his hands and he does not have the proper disinfectants with which to care for himself. The veterinarian should have this information in order to advise his client if the latter is not aware of such danger. The veterinarian is thus in a position to protect himself and to render a greater service to the livestock industry, for he can extend this information to the farmers and aid in the prevention of undulant fever.

We have stressed the disease in cattle as a source of infection for man, but it must be remembered that *Brucella abortus* is pathogenic for nearly all species of domestic animals. Goats, sheep, swine, horses and domesticated birds have been found occasionally to be infected with *Brucella abortus*. The premature expulsion of a fetus from any species is clinical evidence of infectious abortion that should be checked by laboratory tests. Aside from cattle, swine and horses present the greatest danger to man. Many of the porcine strains are extremely pathogenic for the human family, and because of close contact with cattle, swine may transmit very virulent strains to cattle. *Brucella abortus* has been isolated from such lesions of horses as poll-evil and fistula of the withers. Such localized infections in horses should be handled with great care. The blood test and bacteriologic examinations should likewise be

carried out, and are as valuable in detecting and controlling the disease in these species as they are in cattle. The elimination of *Brucella abortus* infection in animals protects the butcher, the meat packer and the meat inspector. The value of the blood test cannot be overestimated.

The third group, in which we have included veterinarians and laboratory workers engaged in research on infectious abortion or in the routine examination of material for *Brucella abortus*, is continually exposed to the infection. Many cases of undulant fever have occurred in such individuals, and although the disease is seldom fatal, it runs a protracted course that has incapacitated the patients for 1 or 2 years, and in certain instances for even a greater period. In the chronicity of the disease lies the seriousness of this infection, and since we have no satisfactory treatment to shorten the course of undulant fever, prophylaxis, such as the disinfection and protection of wounds from invasion by the organism, should be stressed. We see great differences in the susceptibility of individuals who come in direct contact with massive doses of the infection. Certain veterinarians and laboratory workers take no precautions whatever, when they are aware of exposure to the infection, while others, taking the strictest care, develop symptoms of the disease. Individuals possessing a natural immunity may be employed in a laboratory to work with *Brucella abortus* with impunity. In our laboratory we make it a practice to examine the blood of any new helper when he begins his work, and to test his blood every six or eight weeks. We also make a skin test on the individual when he first enters the laboratory. This consists of injecting intracutaneously 0.1 cc. of a suspension containing approximately 5,000,000,000 killed organisms per cc. This gives us valuable information. I believe it is wise to go one step further, as is done in certain European laboratories, where it is a practice to immunize the laboratory workers by injecting, subcutaneously or intracutaneously, small amounts of killed suspensions of *Brucella abortus* and *Brucella melitensis*. It might be well to consider this method of immunization for veterinarians. Killed suspensions of *Brucella abortus* injected into cattle do produce some temporary immunity, but similar experiments on guinea pigs, followed by the injections of living cultures or other infectious material, have failed. Nevertheless, there is some evidence that such injections in man are valuable and perhaps as efficacious as the injections of killed suspensions of *Bacillus typhosus*. The protection may last a long time, or it may be permanent. At present we do not have enough available information to be certain of the value of such a procedure, but indications are favorable. Some interesting information has been accumulated on the immunity acquired by veterinarians. Thomsen,¹⁹ of Denmark, tested the blood from several groups of veterinarians: Those who had practised for more than 1 year; a group that had practised 5 months; a group that had practised 1 month; a group of senior

veterinary students who had never practised. The results he obtained were, respectively, 94, 85, 42 and 0 per cent. Some of these men with positive serums had typical cases of undulant fever, some described symptoms suggestive of the disease, while some denied having had any illness whatsoever. He found also that the serum of 10 out of 16 bacteriologists showed abortus antibodies, and, therefore, suggests the vaccination of young veterinarians, caretakers of animals, animal owners and research workers who come in contact with the disease.

Huddleson and Johnson²⁰ have reported results obtained from testing for abortus agglutinins the serum of 49 veterinarians in Michigan. They found that 57 per cent of the group was positive to the test, and that 26 per cent had a titer of 1 to 100 or higher. Three of the men gave definite evidence of having undulant fever while others either gave vague histories of the disease or denied any such experience. It is evident that this group should be protected and we believe vaccination will afford such protection. Recently Dubois and Sollier²¹ reported results on the prophylactic vaccination of man with heat-killed suspensions of mixed strains of brucella, containing 2,000,000,000 organisms per cc. One hundred and eleven persons exposed by contact and by consuming infective dairy products in from 3 to 8 months after vaccination failed to develop undulant fever, while 2 of 36 similarly exposed individuals not vaccinated contracted the disease.

Although undulant fever is rarely transmitted from patients to those caring for them, there is such a possibility. *Brucella abortus* is isolated from the urine in approximately 10 per cent of the cases. Amoss and Poston²² have recently reported recovering the causative agent from the stools of patients, suggesting alimentary tract infection. This necessitates the careful disposition of these excretions and bacteriologists working with such specimens should consider them a source of danger.

Summary. 1. Sources and modes of infection are described.

2. Data are submitted, indicating that guinea pigs can be infected by feeding them porcine or human strains of *Brucella abortus*, or by placing the cultures on the unabraded skin.

3. The application of 5 per cent lysol, 1 to 1000 solution of bichlorid of mercury, 70 per cent alcohol, or ivory soap and water solution to the skin areas of guinea pigs, 10 minutes, 30 minutes and 4 hours after cultures of *Brucella abortus* had been placed on the unabraded skin, failed to prevent abortion disease.

4. The thermal death time of *Brucella abortus* is discussed and studies on the pasteurization of milk containing this organism are reported. An examination of 205 pasteurized samples of milk and cream showed no infection with *Brucella abortus*. Pasteurization will protect the consumer of dairy products.

5. A method for the control of infectious abortion in domestic animals is described. The value of blood testing and isolating or

eliminating infected animals is emphasized. The importance of eradicating the disease in small communities and on farms where facilities for pasteurization are not available is stressed. Boiling of the milk under such circumstances is satisfactory, but a practice difficult to institute.

6. The vaccination of veterinarians and bacteriologists continuously exposed to *Brucella abortus* is suggested.

7. The proper disposal and care in the examination of urine and feces from patients with undulant fever is emphasized.

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A NEW TYPE OF DUODENAL TUBE TIP.*

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It is the purpose of this article to describe a new type of duodenal tube tip, designed to prevent certain difficulties which occur in nonsurgical biliary tract drainage. In our experience, as well as

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in that of many others, these difficulties have recurred in some cases with any of the duodenal tubes now in use, even under the most expert technique. Our experience is based upon over 2000 drainages, begun 5 years ago under the direction of Dr. Ludwig Kast and continued in the combined Surgical and Medical Gall Bladder Clinic of the New York Post-Graduate Hospital.

A study of the technique of duodenal drainage has indicated that the most common cause of failure has been inability to introduce the tube into the duodenum, the passage of the bucket through the pylorus having been difficult or impossible. Another frequent difficulty has been the regurgitation of the bucket from the duodenum into the stomach, usually following the injection of stimulants such as magnesium sulphate, an occurrence by no means uncommon in those patients having an irritable stomach or duodenum. Difficulty in swallowing the tube has proved a negligible factor.

Credit for the pioneer work in duodenal intubation must be given to Einhorn, Hemmeter and Gross. Further valuable improvements both in instruments and in technique have been contributed by Jutte, Rehfuess, Lyon, Buckstein, Levin, Kohn and Wilkins. Our routine practice has been the use of a metal bucket such as that of Lyons or Rehfuess, which has seemed to us most reliable for the average patient. In difficult cases, however, the Levin catheter-tip tube has sometimes proved more satisfactory.

We have also paid special attention to the maneuver of Dr. Morgenstern in passing the Levin tube under the fluoroscope, by manual manipulation. While the results of this procedure have been spectacular at times, in many cases it has not been successful. The principal difficulty has been the tendency of the tube to loop in the cardiac end of the stomach, above the costal margin, where manipulation is impossible. Moreover the ultimate aim of the technique of duodenal drainage should be a successful drainage without the need of Roentgen ray control, except in cases of suspected organic obstruction of the pylorus.

In view of these difficulties, the author has designed a different type of drainage tube tip, which facilitates passage of the bucket into the duodenum and is more likely to keep it there, even in those patients who are apt to reject the bucket from the duodenum following the use of stimulating fluids. During the past year the new tube has been used successfully in almost all of a series of about 100 cases, most of which had been selected because drainage with other types of tubes proved unsuccessful, in many cases after repeated attempts.

The original tube as designed in 1929 consists of the standard type of tubing which has in place of the usual bucket, a terminal unit of two parts. The proximal of these is a narrow-slotted bucket, attached to a metal ball. $\frac{3}{4}$ inches in diameter, by a thin chain,

1½ inches long. The chain is fastened to the bucket by means of a ball-and-socket joint, the chain and its connections being covered with a waterproof protection which is a section of light, flexible, rubber tubing, tightly tied with silk thread at both ends.

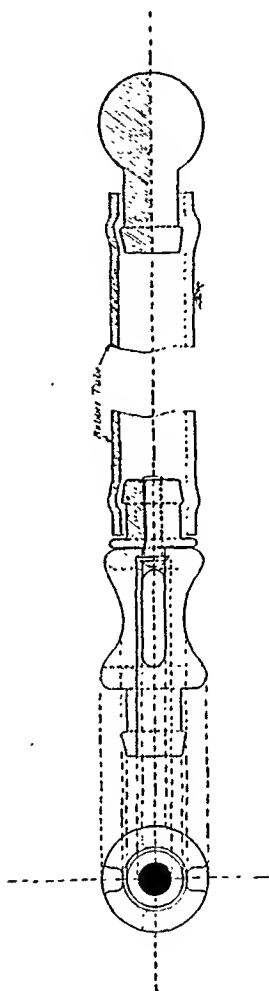


FIG. 1.—Model with shoulders containing grooves for the purpose of preventing obstruction of the slots by collapse of the viscerai walls and adherence to the walls by suction.

The bucket is constructed of metal tubing, $\frac{1}{4}$ inch in diameter, the distal end being turned to enclose the small ball in which the gold-plated chain is imbedded. The other end of the chain is similarly attached to a small piece of metal, square on one end, threaded on the other. The threaded end screws into the brass ball, this arrangement allowing the rubber tubing to be slipped over the chain. The entire unit is gold-plated.

We are now using a similar model with a shorter bucket and swivel joint in the place of the ball-and-socket joint. The ball

has been reduced in size to $\frac{5}{16}$ inch. A further very satisfactory modification of this design eliminates the chain and the swivel joint, the terminal ball being attached to the distal end of the bucket by only the rubber tubing. Shoulders on each end of the bucket, of slightly larger diameter than the tubing, contain longitudinal grooves. This arrangement provides for a free flow of fluid from above or below the bucket, as well as preventing adherence to the mucosal wall by suction, regardless of how constricting the surrounding viscera may be. A special method of tying the thread on the ends of the tubing eliminates knots with their irritation of the esophagus and tendency to untie.

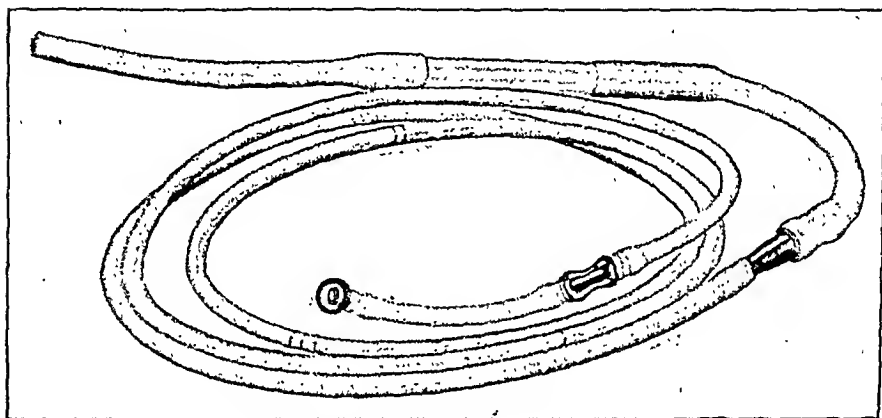


FIG. 2.—Complete tube with glass window.

Materials of which the tip has been constructed include gold and brass, gold-plated. The highly soluble character in hydrochloric acid of brass and most other metals, together with the resultant toxic salts, make the use of an inert metal such as gold essential. Gold-plating is at times not entirely satisfactory, minute defects occur which form an electrochemical couple. The result is rapid corrosion and discoloration of the bucket, the use of buckets having this appearance should never be allowed. A further advantage of gold is found in its specific gravity, which is approximately double that of brass or lead. With a terminal ball of gold, a given weight may be obtained by the use of a ball of half the size otherwise required, which facilitates swallowing and extraction of the tip.

The malleable character of gold renders its use practical from the mechanical standpoint. The cost of a low grade of gold is not greatly in excess of that of inferior metals, the increased expense is offset by its advantages in providing a safe and easily cleaned instrument, which always looks well, and will last indefinitely. Another consideration is the cost of replating and replacing buckets of other types of metal.

The construction of this tube allows greater flexibility and adaptability to irregular surfaces, and to a constricted or spasmodic pyloric ring. The terminal ball acts as a weight, the ball-and-socket or swivel joint eliminates the factor of twisting. The ball being freely carried by the peristaltic action of the stomach to the pyloric orifice enters easily because of its minimum diameter at any angle of entrance. These models can frequently be introduced into the duodenum within 10 minutes with the patient sitting up; when lying on the right side the time of entrance into the duodenum is usually about 20 minutes. In cases of pyloric obstruction a smaller ball may be substituted for the usual size.

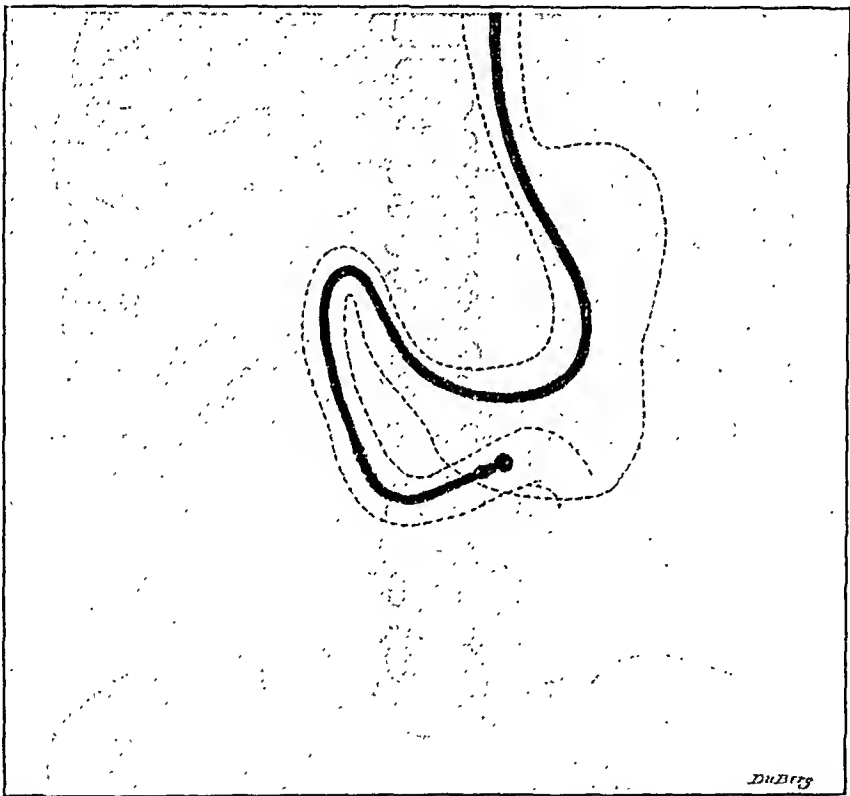


FIG. 3.—Tracing of a roentgenogram, showing tube with bucket in the descending duodenum. Position verified by the ingestion of contrast medium.

Fluoroscopic study has shown the ball to enter the duodenum promptly, drawing the bucket after it. The tube is allowed to descend in the eustomary manner until the 3-ring mark is at the lips of the patient, after which bile is obtained. The weight of the terminal ball retains the position of the bucket after stimulation, even in cases with an irritable duodenum. We have been more successful with the manual introduction of this tube under the fluoroscope than with any other type. Roentgenogram studies of the tube in position, verified by the ingestion of contrast medium,

have been made through the courtesy of Dr. W. H. Meyer, Director of the Department of Roentgenology.

Concentration of the weight of the tip at the end of a flexible section has proved an advantage. Slots in the bucket of approximately the same width as the inner diameter of the tube prevent as far as possible the obstruction by mucus or débris. Rubber tubing of slightly larger caliber than that now in use provides satisfactory resiliency and tends to prevent looping. A section of glass tubing 3 inches long in the syringe end of the tube insures a sterile tip for taking cultures when the terminal section of rubber tubing is temporarily removed.

Summary. Investigation of the technique in over 2000 biliary tract drainages has shown that in most cases in which results were unsatisfactory or the drainage unsuccessful, the cause was either inability to pass the tube through the pylorus or failure of the duodenum to retain the bucket following stimulation.

A type of duodenal tube tip is described which during the past year has greatly facilitated our technique of drainage, even in those cases in which drainage had been previously reported as being unsatisfactory or impossible. Arrangements are being made for the manufacture of this type.

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REVIEWS.

CYTOLOGY AND CELLULAR PATHOLOGY OF THE NERVOUS SYSTEM. Three volumes. By VARIOUS CONTRIBUTORS. Edited by WILDER PENFIELD, Professor of Neurology, and Neurosurgery, McGill University, Montreal. *Vol. I. Neurones, Nerve Sheaths and Nerve Endings. Vol. II. Neuroglia, Microglia, Bloodvessels, Meninges, Pineal, Pituitary, Eye. Vol. III. Neoplasms, Malformations, Reactions.* Pp. 1280; 886 illustrations, 15 in color. New York: Paul B. Hoeber, Inc., 1932. Price, \$30.00.

THESE three volumes, the work of 26 distinguished students of the central nervous system, are a timely and most welcome contribution to the literature of a subject, of interest alike to the general biologist, the neuro-anatomist, the neuropathologist, the neurophysiologist and the clinical neurologist. Within the past few years many new methods have been devised which have made possible a more detailed study of the intimate structure of the nervous organs. The harvest reaped has been very great, so great indeed that today's conception of the structure and function of the nervous system in health and in disease is vastly different from that which prevailed a decade or two since. There are few students of this system who have been able to keep step with the rapid march of progress. In these volumes an excellent account is given to what is known at this time of the microscopic structure of nervous tissue. No one man, alone, could have written this account, and wisely, the editor, himself a well-known investigator, has invited collaborators from various countries. The contributions represent the splendid achievements which have come to us from the great research institutes and the universities of the United States, Canada, Sweden, Germany, Holland, Spain, Great Britain and France. The composition of the work demonstrates the care the editor has exercised in outlining the scope and structure of these volumes. Each chapter is from the pen of a writer who, through his own investigations, is most familiar with the treatment of each subject discussed. Volumes I and II take up the intimate structure of the nerves in health and disease from a general viewpoint. In them the anatomy and physiology of each cell group, or each component part of the nervous system, is described and discussed in turn, thus presenting the foundation necessary to the understanding of the several disease entities. The third volume contains studies of certain pathologic entities, and is noteworthy particularly for its splendid discussion of the neoplastic diseases of the nervous system. In order to avoid repetition descriptions of disease entities which are scattered through the first two volumes are not again discussed in the third volume, but are made readily available through an excellent index.

In Volume I Cowdry (St. Louis) discusses the general character of the neurone, Kappers (Amsterdam) the principles of development of the nervous system and Bielschowsky (Berlin) treats the pathologic changes which nerve cells in general may undergo. This chapter serves as a splendid introduction to the histopathology of nerve cells, and should be mastered by all who wish to become familiar with this difficult subject. De Castro (Madrid) contributes two chapters, one on the sympathetic ganglia, the other on the sensory ganglia of the cranial and spinal nerves; both normal and pathologic conditions are considered. Boeke (Utrecht) describes the sensory and motor nerve endings and Nageotte (Paris) the sheath of the peripheral nerves, the structure of nerves and their degenera-

tion and regeneration. In the last chapter Stöhr (Bonn) gives an account of the nerves of bloodvessels, meninges and other structures.

In Volume II Penfield (Montreal) describes normal and pathologic neuroglia, and Del Rio-Hortega (Madrid), the microglia. The choroid plexus and ependyma are dealt with by Agduhr (Upsala), the cerebrospinal bloodvessels by Cobb (Boston), the meninges by Weed (Baltimore), the pineal gland by Del Rio-Hortega, the hypophysis by Bucy (Chicago), the retina, choroid and sclera by Arey (Chicago), and, finally, the optic nerve and papilla by Cone and McMillan (Montreal).

A large part of Volume III is devoted to the tumors of the nervous system. There are chapters on the primary tumor of the brain by Bailey (Chicago), of the sheaths of the nervous system by Penfield (Montreal), of the spinal cord by Kernohan (Rochester, Minn.), the optic nerve by Verhoeff (Boston), the retina by Grinker (Chicago), the choroid by Friedenwald (Baltimore), the sympathetic nervous system by Bielschowsky (Berlin) and the hypophysis by Bailey. Masson (Montreal) discusses the interesting neural proliferations in the vermiform appendix, and Globus (New York) the malformations of the nervous system. Hydrocephalus and the atrophy of cerebral compression is presented by Penfield and Elvidge (Montreal). The inflammatory cells in the nervous system, a difficult and somewhat controversial subject, is ably presented by Greenfield (London). Finally there is a chapter by Boyd (Winnipeg) on the cells found in the cerebrospinal fluid under normal and abnormal conditions.

There are nearly 900 illustrations, and nearly all of them of exceptional clarity. The index is very satisfactory.

The volumes are fittingly dedicated to the spirit of scientific investigation exemplified in the histologic work of Ramón Y Cajal.

The reviewer would compliment the editor for having well accomplished a difficult task. This work, a truly international undertaking, will be an indispensable handbook for special students of the nervous system, and an invaluable work of reference to those who wish a concise and modern account of its structure.

B. L.

A DIABETIC'S OWN COOK BOOK. By STELLA H. LYONS. With a Foreword by LOGAN CLENDENING. Pp. 94. New York: Alfred A. Knopf, 1932. Price, \$2.00.

THE book is a compilation of menus, recipes and tables of food values. The author is a diabetic who has incorporated into this book her experience with the preparation of food and arrangement of diets. One object of the book is to relieve the patient of the use of the scale and metric measurements. She has in most instances used both metric measurements and their equivalents in household measures. There are, however, menus where only household measurements are employed. This book will be helpful to patients whose physicians are satisfied to have the quantities of food measured with a teaspoon, tablespoon and cup.

L. J.

CAUSATION, DIAGNOSIS AND TREATMENT OF CANCER. The Beaumont Foundation Lectures, Series No. 10. By JAMES EWING, M.D., Professor of Pathology, Cornell University Medical College. Pp. 87. Baltimore: The Williams & Wilkins Company, 1931. Price, \$1.00.

FROM among the welter of newly published books there occasionally arises one which is outstanding. To make the acquaintance of such a book renews one's faith in the value of the printed page.

In this small book is condensed and evaluated our present knowledge of cancer. Throughout the text there are erected for the guidance of those who have eyes which see many sign posts mapping the paths which lead to the future solution of the problem of cancer.

No student or practitioner of medicine can afford not to know this book.
G. W.

A BIBLIOGRAPHY OF THE HONORABLE ROBERT BOYLE, FELLOW OF THE ROYAL SOCIETY. By H. F. FULTON, M.A., (OXON), Formerly Fellow of Magdalen College, Oxford. Pp. 170; illustrated. Oxford: University Press, 1932.

From previous works of Fulton's such as "Physiology" in the *Clio Medica* series, it was so obvious that Robert Boyle was one of his favorites that it is no surprise to see this beautiful bibliography. The plan of the volume is as follows: After the 9-page Preface with some interesting details about Boyle's life and on various bibliographical details, 42 of Boyle's separate works are treated in detail under 197 items. Contributions to other works (mostly the *Philosophical Transactions*) are followed by the various editions of his collected works, with a final chapter of over 100 items of elegies, biographies and commentaries. In the appendices are given lists of Boyle's Lecture Sermons since 1692 and of the Robert Boyle Lectures (founded 1892). While obviously a book chiefly of use as a record, and disclaiming any attempt to deal with Boyle's position in science, it contains, concealed in its explanatory paragraphs, much that is of interest to the amateur of the history of science.
E. K.

PRACTICAL TREATMENT OF SKIN DISEASES. By EDUARD AHLSEWEDE, M.D., New York and Hamburg, Formerly Assistant Physician, University Skin Department, Direction of Professor Unna, Eppendorf Hospital, Hamburg, etc. Pp. 770; 77 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$12.00.

This interesting work is a manual of dermatologic treatment, essentially a formulary containing much valuable information and numbers of prescriptions. It will be of even greater service to the newer generation of dermatologists in supplying them with many of the time-honored tools of the specialty than it will be to the practitioner. The arrangement of the topics is alphabetical under disease names, the illustrations largely devoted to physiotherapeutic apparatus. In the effort to make the work inclusive, such subjects as scarlet fever, which might better have been left to medical texts, have been introduced. The extended use of proprietary and personal names for preparations without adequate explanation of their meaning is a disadvantage. The work expresses very well the essentially local treatment traditions of dermatologic therapy, the management of constipation in acne, for example, being confined to the essentially archaic jalap and mercurial cathartics. Anti-infection vitamins, liver extract, diet in psoriasis, diet in general as a therapeutic agent receive little or no attention. Many conflicts of opinion find their expression rather in a total elimination of the conflicting viewpoints, as for example in the light therapy of psoriasis rather than in a balanced consideration of the pros and cons. The psychogenous dermatoses, important at the moment in our high-tension American life, receive one page with the advice that they be referred to a neurologist. Notwithstanding these easily recognized deficiencies, this book is a useful one which should materially increase the versatility and elegance

of the dermatologist's approach to many even commonplace treatment problems. There are no illustrations of cutaneous diseases, and there is no bibliography so that the tyro and the researcher should not confuse this with a student's text or a scientific monograph.

J. S.

REFLEX ACTIVITY OF THE SPINAL CORD. By R. S. CREED, D. DENNY-BROWN, J. C. ECCLES, E. G. T. LIDDELL and C. S. SHERRINGTON. Pp. 183; 71 illustrations. New York: Oxford University Press, 1932. Price, \$3.25.

In the 6 years that have elapsed since the publication of Fulton's excellent monograph, much light has been thrown on the mechanisms of reflex action. No laboratory has contributed more to that end than that of physiology at Oxford. A review of the subject by Sir Charles Sherrington and his colleagues is to be welcomed as the filling of an urgent need by those best qualified for the task. Within the limits of 165 pages of text, it might seem impossible to write more than an elementary primer or perhaps an analysis of some of the most recent advances in such a field. The book is neither of these things. It is a lucid synopsis of virtually all that is known about the subject today. So skillfully has Dr. Liddell correlated the contributions of his co-authors, that the reader unfamiliar with the material might well mistake it for the work of a single hand. Both for him and for one conversant with all of the 209 papers which comprise the bibliography, the little volume holds compact several hours of delightful and stimulating reading.

G. McC.

CEREBRAL INJURY IN NEW-BORN CHILDREN CONSEQUENT ON BIRTH TRAUMA; WITH AN INQUIRY INTO THE NORMAL AND PATHOLOGIC ANATOMY OF THE NEUROGLIA. By ERIK RYDBERG. Pp. 247; 49 illustrations. Copenhagen: Levin & Munksgaard, 1932.

This monograph is divided into two parts: one dealing with the anatomy of the neuroglia in the infant brain and the other with the study of the brain after birth trauma. Particular attention is given to the characteristics of the matrix tissue, a portion of the infant brain which requires still further study. Rydberg differentiates unorthodoxly between small and large spongioblasts. He comes to the conclusion further that the microglia is of ectodermal rather than of mesodermal origin (as proved by Hortega), and that it is derived from the ependyma mainly, but in part also from the vascular elements or the leptomeninges. In opposition to the present concept of neuroglia, he favors the view that "the astrocytes appear as widely ramified cells with an extensive plexiform extension of the expansions, and a dense reticulum becomes visible which is connected with the expansions of both the astrocytes and the oligoglia cells, forming a direct continuation of them." Rydberg takes up also the question of the identity of the embryonic fat granule cells. He found that the fat was mostly extracellular, surrounding astrocytes, oligodendroglia and microglia; rarely the microglia, and presumably had to do with myelinization.

The matrix tissue needs study and the author has made a serious attempt to unravel its characteristics. However, his conclusions concerning the microglia and the glial reticulum cannot be accepted without better proof; the contrary evidence is too convincing.

The second portion of the monograph deals with a study of 100 fetuses born at term or within 10 days after birth. Gross hemorrhages were

found in 58 cases, meningeal in 56, cerebral in 28 and subependymal in 11. Rydberg attributes the hemorrhages to "a primary circulatory obstruction in the brain, due to local brain pressure." Compression of the head causes an increased intracranial pressure, which is followed by a secondary rise in blood pressure. If a sudden fall in intracranial pressure causes a marked difference between intravascular and extravascular pressure, hemorrhage results. "This may happen at the moment of the cessation of a pain, if the fetal blood pressure is raised to a high level."

The monograph is written in English. It is well illustrated. The first portion seems more valuable than the second. The conclusions reached by the author are open to question. B. A.

RECENT ADVANCES IN PATHOLOGY. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to the Royal Free Hospital, and LAWRENCE P. GARROD, M.A., M.B., B.CH. (CAMB.), M.R.C.P. (LOND.), Bacteriologist and Lecturer in Bacteriology, late Demonstrator of Pathology, St. Bartholomew's Hospital. Pp. 392; 67 illustrations. Philadelphia: P. Blakeston's Son & Co., 1932. Price, \$3.50.

THE "Recent Advances" series, which now covers 25 subjects, has received here one of its most important additions, forming with "Surgery," "Children," "Bacteriology" and "Chemotherapy" larger books than the rest of the series. Of the 15 chapters "The Reticulo-endothelial System," "The Ductless Glands," 4 on cancer research, 2 on the cardiovascular system and 2 on Bright's disease are the most important. It is obvious that the authors have achieved their main purpose of presenting "recently acquired knowledge of disease processes in a form useful to the student of medicine." In fact, their success raises the question as to whether this is not a better "follow-up" method than the costlier loose-leaf systems that are more in vogue in this country. While occasional slips are noted, such as the confusion of open and closed circulation in the spleen (p. 29), the information is accurate and the material well chosen. The American literature is well represented—possibly somewhat at the cost of the German—and the photomicrographic illustrations really illustrate. The British ability for sane evaluation and clear elucidation has borne good fruit in this useful volume. E. K.

ITALIAN MEDICINE, VOL. 6 OF CLIO MEDICA. By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine, Royal University of Padua, Italy. Translated by E. B. KRUMBHAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 134; 11 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.

IN this small volume, the author has made easily available to the busy practitioner and student of medicine many interesting trends in the development of medical thought in Italy which heretofore were only to be found, at the expense of a considerable amount of labor, scattered throughout the voluminous literature of medical history. The history of Italian medicine is the framework of medical history in general and is obviously too vast and too complex to be concentrated in all its interesting details in one small volume. The author, one of the leading medical historians of modern times, has selected the most important and significant facts in each period and has presented them in a readable and concise form with none of the earmarks of the choppy outline and none of the characteristics of the pedantic treatise. The origin of Italian medicine in Southern Italy

is traced from the philosophic schools of Greece and followed through the schools of Monte Cassino and Salerno, the Universities, the Renaissance and so on to modern times. Throughout the book, the development of medicine is skillfully correlated with social and political history, and the evolution of art and literature.

A. C.

LEONARDO DA VINCI. By PROF. DR. SIGMUND FREUD, LL.D. (Univ. of Vienna). Translated by A. A. BRILL, PH.B., M.D., Lecturer in Psychoanalysis and the Psychosexual Sciences, Columbia University. Pp. 130; illustrated. New York: Dodd, Mead & Co., 1932. Price, \$3.00.

A CONTINUATION of Freud's "valiant effort" to solve the problem of sexuality, this book aims to explain Leonardo's inexplicable genius, at the same time giving a clinical demonstration of the author's psychosexual theories.

According to Scognamiglio, Leonardo once wrote about his childhood as follows: "It seems that it had been destined before that I should occupy myself so thoroughly with the vulture, for it comes to my mind as a very early memory, when I was still in the cradle, a vulture came down to me, he opened my mouth with his tail and struck me a few times with his tail against my lips." From this scene, which Freud regards as a phantasy of later life transferred to infancy, the author says that he will attempt to fill in the gaps of Leonardo's life story by analysis of the phantasy. With his well-known ability to find sexual explanations, the author translates the phantasy erotically, the vulture's tail, coda, being a substitutive designation of the male member, suggesting the act of *fellatio*. This is, however, dismissed by him as a natural occurrence of harmless origin, reminiscent of nursing. On similar grounds, the vulture is thought to represent the mother, as it does in Egyptian mythology, whose vulture-headed motherly deity, Mut, is suggested as related to "Mutter." In the writings of the Church Fathers in connection with Virgin birth, vultures were regarded as all females (impregnation occurring by the wind); hence Leonardo, the illegitimate child, formed the phantasy of the vulture-child with a mother but no father. On grounds of such solidity the author feels he can fill in a gap in Leonardo's childhood, to show that his reception in his father's house (known to be before the age of 5 years) must have been after the decisive years of his "infantile sexual investigation" when he formed his mother-cherishing, father-missing complex. Further examples of the author's expressed intention to fill in gaps, however, are not apparent on perusal of later pages.

Through the erotic relations to the mother, the author reasons that Leonardo became homosexual, giving as evidence his love for fine apparel and his good-looking male pupils, though he admits that proof is quite lacking. Later he states that "Sexual repression caused him to sublimate his libido into a thirst for knowledge, which conditioned his sexual inactivity for his entire later life." Even the author admits that two of Leonardo's characteristics remain unexplained, "First, his particular tendency to repress his impulses, and second, his extraordinary ability to sublimate the primitive impulses."

To those who enthusiastically follow this modern pioneer of sexual philosophy, this interpretation will doubtless be sufficient and absorbing. The cover advertisement even speaks of it as one of the outstanding achievements in the field of psychology. The larger number of readers, unsympathetic and critical, will find that it confirms their skepticism if their curiosity leads them to consider it at all. Few, indeed, will be converted by such phantastical, far-fetched and often loose and illogical reasoning.

E. K.

SURGERY OF THE CHEST. By GEORGE F. STRAUB, M.D., F.A.C.S. Pp. 475; 341 illustrations, including 68 color plates. Springfield, Ill.: Charles C Thomas, 1932. Price, \$10.50.

EXCELLENT chapters on the history of chest surgery and the principles of the physiology and surgical physiopathology of the chest precede discussion of the Roentgen ray and bronchoscopy in the diagnosis of intrathoracic lesions. Two chapters, each adequately illustrated, show the general principles of the technique of intrathoracic operations, including anesthesia. His description of the operative treatment of tuberculosis shows a wide experience with the method. In the discussion of acute empyema he does not mention the modern methods of tidal drainage which are now in common use in this country. Very little space is given to the treatment of lung abscess and bronchiectasis. An excellently written chapter describes the surgery of the heart. Surgery of the mediastinum is treated more completely than in most other one-volume books. The author illustrates profusely the various operative methods, drawing largely from the German literature. The final chapter in the book is devoted to the surgical treatment of angina pectoris and asthma by sympathetic nerve ganglion resection.

The book represents a valuable addition to the literature on the surgery of the chest. It is up to date in most particulars and is extremely well illustrated. No references are quoted directly but a bibliography is included before the index. The author writes with an easy style and the printing and binding are in excellent taste, all of which combine to recommend the work to those interested in obtaining a knowledge of this branch of surgery.

L. F.

CANCER: WHAT EVERYONE SHOULD KNOW ABOUT IT. By JAMES A. TOBEY, DR. P.H. With Introduction by JOSEPH COLT BLOODGOOD, M.D., and H. L. MENCKEN. Pp. 323; 17 illustrations. New York: Alfred A. Knopf, 1932. Price, \$3.00.

THIS book, prepared to assist in the campaign for the "Control of Cancer," is intended chiefly for the general public. In the campaign whose foundation stone is "come early and hope to be cured," we may have arrived at the point where its evaluation as a means of diminishing the incidence of cancer can soon be determined.

In criticism of the book it might be said that its size and cost may lessen its popularity, that it is discursive, carrying the reader into many entertaining but unnecessary by-paths, and that it gives the impression of inconsistency and contradiction by overemphasizing the curability of a disease shown afterward to be really very fatal.

J. McF.

LA MALADIE DE BOECK. By A. KISSMEYER, Médecin de l'Institut Finsen. Preface by DR. J. DARIER. Pp. 147; 67 illustrations. Copenhagen, Levin and Munksgaard, 1932.

THE protean morbid anatomic changes on the skin and histology are covered exhaustively in an authoritative manner. The newer information about bone lesions is particularly needed and welcome. The author stems the current trend to regard sarcoid as a tuberculid, criticizing the validity of tubercle bacillus findings, and even hinting at such other granulomas as leprosy as a causative factor.

F. W.

THE CAMBRIDGE MEDICAL SCHOOL. By SIR HUMPHRY DAVY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., HON. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, etc. Pp. 235; illustrated. New York: The Macmillan Company, 1932. Price, \$5.00.

To those who wish to follow the thread of British medical education through the tangled skein of their medical progress this book will prove more helpful as well as vastly more entertaining than the more direct educational statements. Written in the author's well known charming style and with full regard for the principle that personalities are more intriguing to the average reader than abstractions or pedagogical events, the book first tells the general story of the Cambridge medical and then gives short accounts of its various departments. To the historically minded the earlier story will perhaps prove the more interesting, though the larger part of the book contains lengthier chapters about the various departments, especially the seven preclinical chairs, that permit more adequate and satisfactory treatment. Lists of the holders of the various chairs are valuable both for reference and as showing how great may be the influence of one mind, both in quality and in the number of years that it is exerted. The well chosen illustrations complete the satisfaction with which one handles this volume. E. K.

BUILDERS OF AMERICAN MEDICINE. Being a Collection of Original Papers read before the VICTOR C. VAUGHAN Society of the University of Michigan Medical School. Pp. 243; illustrated. Ann Arbor: George Wahr, 1932.

THE portrayal of 12 noted American physicians in this book is in itself a real addition to American medical history; but it possesses still further importance as an example of the constructive interest that medical school seniors can exhibit. The Victor C. Vaughan Society is to be congratulated not only on the historical acumen and literary ability shown by the authors of the 12 chapters here selected from their fortnightly meetings, but also on its successes in outlining to other medical students a valuable approach to the fascinations of medical history. E. K.

BOOKS RECEIVED.

NEW BOOKS.

A Handbook of Experimental Pathology. By GEORGE WAGONER, M.D., Associate in Pathology, and R. PHILIP CUSTER, M.D., Associate in Research Pathology, The School of Medicine, University of Pennsylvania. Pp. 160; 22 illustrations, various tables and charts. Springfield, Ill: Charles C Thomas, 1932. Price, \$4.00.

Clinical Gynecology. By C. JEFF MILLER, M.D., Professor of Gynecology, Tulane University School of Medicine; Chief of the Department of Gynecology of Touro Infirmary, etc. Pp. 560; 134 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$10.00.

Synopsis of Gynecology. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology, Washington University Medical School, etc.; and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Pp. 227; 110 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$2.75.

- Clinical Laboratory Manual for Nurses and Technicians.* By SISTER ALMA, Chief Laboratory Technician and Instructor of Nurses at St. Thomas Hospital, Akron. Pp. 159; 55 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$1.75.
- Antony van Leeuwenhoek and his "Little Animals."* By CLIFFORD DOBELL, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accademia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Pp. 435; illustrated. New York: Harcourt, Brace & Co., 1932.
- Children's Tonsils In and Out.* By ALBERT D. KAISER, M.D., Associate Professor of Pediatrics, University of Rochester Medical School, etc. Pp. 307; 25 figures. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.
- Alcohol and Man.* Edited by HAVEN EMERSON, M.D., De Lamar Institute of Public Health, Columbia University. Associate Editors: HENRY A. CHRISTIAN, M.D., and REID HUNT, M.D., Harvard University; ARTHUR HUNTER, LL.D., F.A.C.S., New York Life Insurance Company; CHARLES C. LIEB, M.D., Columbia University; WALTER R. MILES, Ph.D., Yale University; ERNEST G. STILLMAN, M.D., Rockefeller Institute for Medical Research. Pp. 451; illustrated with tables. New York: The Macmillan Company, 1932. Price, \$3.50.
- Causation, Diagnosis and Treatment of Cancer.* The Beaumont Foundation Lectures, Series No. 10. By JAMES EWING, M.D., Professor of Pathology, Cornell University Medical College. Pp. 87. Baltimore: The Williams & Wilkins Company, 1931. Price, \$1.00. For review see p. 116.
- Publications of the Committee on the Costs of Medical Care: No. 19. University Student Health Services.* A Study of Organization, Services Rendered, and Costs in Cornell University, Yale University, the University of Michigan, the University of Minnesota, the University of California, and Oregon State Agricultural College. By DON M. GRISWOLD, M.D., Dr. P.H., and HAZEL I. SPICER. Pp. 114; illustrated with tables. No. 20. *A Community Medical Service Organized Under Industrial Auspices in Roanoke Rapids, North Carolina.* By I. S. FALK, Ph.D., DON M. GRISWOLD, M.D., Dr. P.H., and HAZEL I. SPICER. With Reports on Certain Phases of the Organization by DAVID RIESMAN, M.D., Sc.D., and GEORGE P. MULLER, M.D. Pp. 105; illustrated with tables. Chicago: The University of Chicago Press, 1932. Price, 90 cents each.
- Practical Obstetrics.* By P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College; Chief Obstetrician, Jefferson Medical College Hospital. Assisted by THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College. Pp. 730; 516 illustrations, including 21 colored plates. Philadelphia: F. A. Davis Company, 1932. Price, \$8.00.
- Transactions of the American Otological Society, Inc. Vol. XXII.* Sixty-fifth Annual Meeting, Atlantic City, May 17 and 18, 1932. Published by the Society, 1932. Pp. 376; illustrated.

NEW EDITIONS.

- Injuries of the Eye.* By HARRY VANDERBILT WÜRDEMAN, M.D., Sc.D., F.A.C.S., Colonel, Medical Reserve Corps; Flight Surgeon, Air Corps, U. S. Army, etc. Pp. 900; 236 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1932. Price, \$13.50.

The second edition of this book is a complete treatise on injuries of the eye and their treatment. The more recent original literature is included.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Quantitative Aspects of Iron Deficiency in Hypochromic Anemia: The Parenteral Administration of Iron.—During the past few years a certain amount of information has been derived from various studies which indicate that many forms of hypochromic anemia depend chiefly on deficiency of iron. In the present study of HEATH, STRAUSS and CASTLE (*J. Clin. Invest.*, 1932, 11, 1293) two purposes were undertaken; first, to compare the doses of iron given parenterally with that given by mouth, and, second, to determine the fate of iron administered parenterally in order to establish a quantitative basis for the better knowledge of this type of deficiency. For the purpose of the investigation, 17 patients with hypochromic anemia were studied most completely. It was found that 1000 mg. of metallic iron given orally is approximately equivalent, from the point of view of the building of blood, to 32 mg. of iron given parenterally. The amount of iron given in this way represented quite closely the amount of iron gained in the circulating hemoglobin and is used in the building of new hemoglobin. For several reasons the authors think it inadvisable to give such large doses of iron parenterally and state that it is undesirable to give the iron this way rather than by mouth. They conclude from these studies that certain types of hypochromic anemia are dependent upon a deficiency of iron which prevents adequate hemoglobin formation.

Relationship Between Acute Liver Injury Induced by Alcohol, Retention in Plasma of Phenoltetrachlorophthalein and Elimination of Phenolsulphonephthalein.—Several months ago in this section was recorded some observations which have been made on the effect of liver injury and the elimination of phenolsulphonephthalein. In this connection it was shown that animals which were given alcohol, which presumably injured the liver, had a high elimination of phenolsulphonephthalein and that despite a concomitant nephritis in an occasional animal. MACNIDER (*Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 78) has continued his studies on this problem and has reported upon a series of animals who were

kept in a state of semialeoholic anesthesia as a result of the repeated introduction from time to time of 10 to 15 cc. of 40 per cent of ethyl alcohol for 12 hours. Eight experimental animals were used and 4 controls, in order to study if there was any relationship between the percentage of retention and rate of disappearance of phenoltetraehlorphthalein from the plasma and the percentage of phenolsulphonephthalein elimination during acute liver injury. It was found that in the control animal elimination of phenolsulphonephthalein was 66 per cent in a typical observation and the concentration of phenoltetraehlorphthalein was 8 per cent. An excised liver specimen was entirely normal. A sample experiment with an experimental animal showed a phenoltetraehlorphthalein concentration of 16 per cent and a retention of 7 per cent of the dye at the end of an hour. Elimination of phenolsulphonephthalein was 83 per cent. The biopsy of the livers of these dogs exhibited marked edema, failure of the nuclei to stain normally and the presence of certain amounts of stainable lipid material which involved chiefly the periphery of the lobules. By this method of experimentation, using phenoltetraehlorphthalein, there was shown to be a definite relation between the degree of liver injury and renal elimination of phenolsulphonephthalein.

SURGERY

UNDER THE CHARGE OF

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C. G. JOHNSTON, M.S., M.D.,

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Water Balance.—The fluid requirements of the surgical patient has within recent years attracted the attention of the surgeon. The patient may be unable to swallow fluids as the result of a lesion of the esophagus so that dehydration results from mere fluid restriction. Such dehydration if not too extensive can be corrected by the simple ingestion of water (AUSTIN and RAVDIN, *Trans. Coll. Phys., Phila.*, 1931, 53, 10). On the other hand, besides simple restriction there may be a marked loss of fluid either by vomiting or from a fistula. Under such circumstances there is not only fluid loss but a loss of salt at the same time. In the acute abdominal crises of an obstructive or suppurative character, in extensive superficial burns, and in fistulae of the gastrointestinal tract, the maintenance of an adequate fluid intake and salt balance becomes a matter of paramount importance (ORR, *Am. J. Surg.*, 1932, 18, 279). Not only is the loss of fluid from vomiting, denuded areas, and fistulae of importance, but the loss of fluid through the skin and lungs is equally important. WILEY and NEWBURGH (*J. Clin. Invest.*, 1931, 10, 689) have made comparisons of the sources of supply and routes by which fluid is lost from the body. These authors studied

the relationship between the environment and the basal insensible loss of weight. They were able to calculate the insensible loss of water and found that in the case of the nude subject, the heat lost by the vaporization of water increased with environmental temperature and decreased with increasing humidity. With a clothed individual changing humidity did not affect the amount of heat vaporized, but this value was still influenced by temperature. In a subsequent study NEWBURGH, WILEY and LASHMET (*J. Clin. Invest.*, 1931, 10, 703) found that the water vapor in a 24-hour period carried with it 24 per cent of the total heat production. Later WILEY and NEWBURGH (*J. Clin. Invest.*, 1931, 10, 723) showed that the mechanism which regulates the water content of even the normal individual is extremely labile. These authors have shown that the common clinical method of studying the water exchange by comparing the fluid ingested with the urine and other easily calculated output is erroneous. The insensible loss of water through the skin and lungs was often greater than the loss of fluid through the kidneys. The water of oxidation varied from 30 per cent to 75 per cent of the water eliminated in the urine. From their studies they conclude that none of the factors involved in the water exchange can be omitted if any accurate knowledge of water balance is to be obtained. COLLIER and MADDOCK (*J. Am. Med. Assn.*, 1932, 99, 875) on the basis of Wiley and Newburgh's work have studied the insensible loss of fluid in surgical patients. In a study of 18 patients these authors found that during operation and a 4-hour postoperative period the average loss of fluid amounted 1000 cc. Of this amount by far the greater amount (700 cc.) resulted from loss by perspiration and by the insensible loss. These studies indicate in a striking manner the strain placed on the patient's water stores during and after operation. A series of papers by GAMBLE (*New England J. Med.*, 1929, 201, 909), HADEN and ORR (*New York State J. Med.*, 1930, 30, 1161) have stressed the importance of the salt loss which is usually associated with fluid loss in surgical patients. The major ions lost are sodium, chlorid and bicarbonate. The persistent loss of these ions results in a disturbance of the acid-base balance. Whether the final condition is one of alkalosis or acidosis depends on the degree to which acid or base ions are lost. With either condition there may be an associated ketosis. Simple hemoglobin or hematocrit estimations are useful methods in determining the degree of dehydration beyond the examination of the texture of the skin and mucous membranes and the urinary output. Valuable also are the methods for studying serum protein. The PAGE and VAN SLYKE method (*J. Am. Med. Assn.*, 1932, 99, 1344) is simple and probably much more accurate than is the determination of serum protein by the refractometer. Recently DOLCH and POECHMULLER (*Hoppe-Seyler's Zeitsch.*, 1931, 195, 28) have described a new method for determining the water in the blood and this may prove a valuable addition to our other methods of determining fluid requirements. DRAKE, MARSH and GAMBLE (*Am. J. Dis. Child.*, 1930, 40, 705) have in a very interesting article shown that, in treating dehydration in which there is an associated disturbance of the acid-base balance, it is more important first to correct dehydration before attempting to correct blood reaction. In fact, in the majority of instances the correction of the dehydration and salt loss will at the same time correct the acid-base disturbance.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Fever Therapy of Neurological Diseases With Pyrifer.—Presenting a critical analysis of the results obtained in 130 patients who were observed for from 1 to 4 years after treatment with pyrifer, out of a total of 220 patients to whom this agent was administered, MANDL and SPERLING (*Med. Klin.*, 1932, 28, 620) submit the following conclusions: Pyrifer constitutes no advance in the therapy of progressive general paralysis. Although one can produce complete remissions, these are, however, not lasting. The agent is of value in these cases only as a substitute for malaria or relapsing fever therapy, when contraindicated or impossible. The best results from the use of pyrifer are obtained in tabes dorsalis. In those cases, however, where there are serious changes in the spinal fluid, malaria therapy is preferable. Pyrifer treatment is contraindicated in cases of tabes dorsalis of the severe atrophic-atactic forms and in the presence of optic atrophy. The results are promising in cases of cerebral spinal syphilis which are not of long duration and which do not show irreparable damage. The influence of pyrifer on the spinal fluid in general paralysis is less profound and less lasting than is that of malaria treatment. It more nearly approaches malaria treatment, however, in its influence upon the spinal fluid in tabes and cerebrospinal lues. Pyrifer acts favorably upon the individual recrudescences of multiple sclerosis and perhaps may ward off progress of the disease for a few years, but it is not capable of preventing new recurrences and it is contraindicated in the very acute ones and useless in the severe chronic forms. The results of its use are questionable in Parkinsonism and schizophrenia. The best results are obtained in the syphilitic lesions when pyrifer treatment is combined with the administration of neoarsphenamin. If the proper technique be employed and the indications and contraindications be observed, the use of pyrifer is without danger.

Ephedrin Treatment of Narcolepsy.—In view of the general failure of all previous attempts to treat narcolepsy and of the recent favorable results reported from the administration of ephedrin, COLLINS (*Ann. Int. Med.*, 1932, 5, 1289) employed it in 2 patients under conditions of well-controlled observation. He reports complete control of the symptoms in both patients which control became manifest almost immediately after the beginning of the therapy. In both instances, however, it was necessary to place the patient upon continued administration of the drug in order to maintain control. He states that

the best results are obtained by administering the drug orally, 3 times a day, in doses of 0.025 to 0.05 gm. ($\frac{3}{8}$ to $\frac{3}{4}$ grain). The best times for administration seem to be at about 8 A.M., noon and 4 P.M. The time of the latter dose is especially important in order to avoid overstimulation of the patient which may persist into the normal sleep period if the drug be administered later in the day. It is wisest to begin with the smaller dose and to increase until the minimal effective dose is determined for each individual patient. Larger doses than the maximum stated seem occasionally to be required but were not necessary in either of the patients who were the subjects of these observations.

On the Action of the So-called Circulation Hormone Upon Vascular Tonus.—SCHRETZENMAYR (*Ztschr. f. Kreislaufforsch.*, 1932, 24, 225) conducted a series of comparative experiments upon intact animals for the purpose of studying the actions upon the tone of the vessels of the following so-called hormones: eutonon, myoston, lacarnol, padutin; and of comparing them with the actions of pure adenosin phosphate. He finds that the four so-called hormones are similar in their actions to the extent that these actions are exerted upon the periphery where they produce a greater or lesser degree of reduction in the tone of the arteries in the extremities, the intestinal tract and the kidney. Both quantitative and qualitative differences occur, however, in the actions of these substances. Eutonon can be shown pharmacologically to exert three distinct actions—one like cholin, a sympathomimetic action and a direct action producing relaxation of smooth muscle. Whether these actions are due to a single substance or to different substances contained in eutonon has not been established, but the latter interpretation seems the more probable since no one substance so far known possesses these three dissimilar properties. Myoston and lacarnol resemble adenosin phosphate in their capacity to diminish vascular tone. Myoston, however, also contains a sympathomimetic component. Padutin on the other hand exerts a direct muscular depressant action on the arterioles. Both adenosin phosphate and the several hormone preparations are capable of promptly antagonizing the disturbances in cardiac rhythm which are produced by gynergen, barium and calcium. From these comparative studies the author feels that future therapy of the spastic disorders of the bloodvessels will be concerned chiefly with the use of adenosin phosphate rather than of the so-called circulatory hormones.

The Treatment of Thyrotoxicosis With Hydrofluoric Acid.—GORLITZER (*Med. Klin.*, 1932, 28, 717) reviews the well-known depressant influence of iodine upon the basal metabolism and reports his own experiments and those of others which show that all of the halogens exert a similar influence, fluorine being by far the most active. He also presents evidence to show that fluorine can be absorbed through the unbroken skin in the form of dilute solutions of hydrofluoric acid. On the basis of these considerations, the author has treated a group of patients suffering from thyrotoxicosis by a series of baths in dilute hydrofluoric acid. The baths were given at an average temperature of 30° C. for a duration of 20 minutes and contained 30 cc. of concentrated hydrofluoric acid in 200 liters of water. Slight variations were made in the

temperature of the baths to suit individual need. No harmful results whatsoever and no discomfort were produced by these baths. The number of baths employed varied for different patients between 4 and 20. In all 24 patients were treated in this manner and the effects of the treatment were controlled both by careful recording of the clinical signs and by changes in the basal metabolism and the body weight. All patients derived considerable improvement from the treatment, many of them having the basal metabolism brought down in a significant manner, but in no instance to normal. In this latter group of patients there was generally also a significant gain in weight. The effects of the treatment seemed to be fairly lasting as determined by adequate follow-up studies. In a few of the patients the baths alone were insufficient to bring about sufficient measure of clinical improvement and reduction of basal metabolism and in these operative procedures were undertaken after which repetition of the baths proved effective. The author cautions concerning the difficulty of handling hydrofluoric acid in its concentrated form and warns that the bath tub must be lined with an impervious layer of rubber in order to prevent the action of acid upon the tub wall.

PEDIATRICS

UNDER THE CHARGE OF

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Hemophilia.—BIRCH (*J. Am. Med. Assn.*, 1932, 99, 1566) studied 35 cases of hemophilia. The ages ranged from the newborn to 52 years. Of these cases 7 were sporadic, while 28 had a definite family history. The histories of 20 families were traced. These consisted of from 4 to 7 generations. An analysis of these histories shows that persons with hemophilia have more daughters than sons, while transmitters have more sons than daughters. Over 71 per cent of the transmitters' sons had hemophilia. Only 10 to 15 per cent of the transmitters' daughters had at least 1 normal son and no hemophilic sons. Of the hemophilic daughters, only 3 to 7 per cent had at least 1 normal son and no hemophilic sons. Nineteen patients had been receiving ovarian therapy for more than 6 months; 9 of these showed a good response, and 9 showed definite but less marked improvement, while the condition of 1 remained unchanged. The response was both general and specific. The general improvement was shown by an increase in weight, hemoglobin and vitality. The specific response was shown by a decrease in number and severity of hemorrhages and a lowering of the coagulation time. The prolongation of the coagulation time in hemophilia is due to increase in the resistance of the blood platelets, for when this resistance is overcome the blood clots in normal time. The blood of a person with hemophilia is morphologically normal. The red cells and hemoglobin may show a secondary anemia, the degree of which depends on the extent and recency of hemorrhage. The white

cells, especially the polymorphonuclear neutrophils, are increased following confined hemorrhages. The thrombocytes are present in normal number, and their morphology does not differ from the normal. The resistance of the thrombocytes is greatly increased, and when this resistance is overcome the blood clots in normal time. This shows that the prolongation of the coagulation time is due to the increased resistance of the blood platelets. If the clotting time of the blood is in excess of 1 hour, the red cells settle to the bottom, leaving blood plasma above. In a general way, the sooner sedimentation begins, the longer the clotting time will be. Roughly speaking, the severity of the hemophilia is in direct proportion to the length of the clotting time. In 1 patient with a serious hemorrhage the coagulation time was in excess of 45 minutes. Patients are relatively safe if the coagulation time does not exceed 1 hour.

Congenital Syphilis.—ATLEE and TYSON (*Am. J. Dis. Child.*, 1932, 44, 718) followed 107 babies of syphilitic mothers in their clinic for varying lengths of time. The condition was checked by studies of the blood and by clinical examination. Some of these babies received anti-syphilitic treatment. Some babies were not considered as being in need of antisyphilitic treatment or were not treated because of poor co-operation of the parents. In analyzing the result of treatment it was found that in not 1 infant that received at least 1 full course of injections, with regular attendance at the clinic, did any signs or symptoms, serologic or clinical, of congenital syphilis become manifest during the period of observation. The few babies developing symptoms or showing a 4+ Wassermann reactions during their first year had received little or no treatment, and their attendance at the clinic had been irregular. The general condition of the patients followed, when last seen, were extremely good in the great majority of instances. In a few babies whose mothers failed to follow the dietary instructions rickets had developed. There was 1 case in which it was interesting to note that a negative Wassermann should not be relied on as a proof of cure unless corroborated by other data. A greater number of patients than presented in this series must be studied in order to prove the point that is emphasized in this presentation. This is that this minimum amount of treatment, started immediately after birth, is sufficient to cure congenital syphilis in this symptomless stage, which is probably the equivalent of the early primary stage of the disease. The main objection raised to prolonged treatment of these babies lies in the fact that it is impossible to tell at birth which babies are going to develop the disease and which are going to escape it. Those that would escape it might be injured to a certain extent by the intensive treatment advocated by most syphilographers. The authors' experience is that babies who show definite signs of syphilis at birth do not survive even though treated immediately. They feel that a positive Wassermann reaction of the cord blood is sufficient evidence to warrant early antisyphilitic treatment. On the other hand, they feel that a negative Wassermann reaction of the cord blood in a child whose mother is definitely syphilitic is not sufficient evidence that the baby will escape congenital syphilis, and the treatment should be given. In this way a high percentage of cures will result from treatment continued over a period of 14 weeks.

The Newer Conception of Diphtheria Immunization.—STRONG (*Arch. Ped.*, 1932, 49, 614) states that all children, excepting those showing decided allergic tendencies, should be given the benefit of active immunization against diphtheria during preschool ages of from 6 months to 6 years without a preliminary Schick test. He recommended the administration of not less than 2 or more than 3 1-cc. doses of diphtheria toxoid or the Ramon anatoxin at intervals of 3 weeks. Children of school age and adults show more local and general reactions to the bacterial protein of toxoid. So that an intradermal test for sensitiveness should be performed before administering the immunizing injections. If evidence of sensitiveness appears within 3 days after the intradermal test, the doses of toxoid should be changed and given 0.1, 0.25, 0.5, 1 and 0.1 cc. of diphtheria toxoid at intervals of 1 week instead of 3. The great susceptibility of the preschool child justifies the elimination of the preliminary Schick test, but it is desirable that this preliminary test be performed on older children, especially in the cities where many children will be found who have acquired an immunity. Among rural children there is a greater susceptibility to diphtheria as evidenced by the greater frequency of positive Schick tests. As argument in favor of the toxoid over the toxin-antitoxin as an immunizing agent it is claimed that the toxoid is from 20 to 30 per cent more effective even in the 2-dose administration. It contains no serum to sensitize to later therapeutic sera. It contains no free toxin, and is more stable and is not affected by freezing. It is believed that many of the difficulties of immunization have been obliterated by this newer development.

DERMATOLOGY AND SYPHILIS

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The Life History of the Treponema Pallidum.—After a thorough analysis of the past and present concepts in regard to the etiology and pathogenesis of syphilis, INGRAHAM (*Am. J. Syph.*, 1932, 16, 155), while not depreciating the great strides that have been made in the last 30 years, feels that our knowledge of this disease, today, leaves much to be desired. When one considers the long and tedious treatment that is necessary to effect a "clinical cure" even in an early case, and when one realizes, as clinical and pathologic studies have so often pointed out, that a conservative physician of the present generation can guarantee no patient freedom from relapse even after the most

vigorous and prolonged treatment, this notwithstanding the apparent specificity of the arsphenamins for the *Treponema pallidum*, it becomes obvious that a certain refinement of our present-day methods, were such possible, would not be amiss. It is reasonable to suppose that this improvement would be realized most rapidly through a better understanding of the life history of the microorganism causing the disease. Since Schaudinn succeeded in identifying the *Treponema pallidum*, in 1905, and Noguchi, 6 years later, apparently obtained pure cultures of the microorganism which were virulent, it has become customary to explain the peculiar characteristics of this disease, such as the long incubation periods, the symptomless latent stages, the almost sterile but none the less destructive tertiary lesions, as some unusual reaction on the part of the immunity mechanism of the host which strives with great difficulty, and often unsuccessfully, to destroy the acclimated spirochete. Such hypotheses are difficult to prove or to disprove. Under the circumstances, it seems worth while to consider the supposition that the spirochete of syphilis may perform some type of a cycle of evolution, especially since it has been proved that the related microorganisms, the *Trypanosomata*, do so, and since it has been suggested in the cases of certain other of the parasitic genera of the Spirochetaceæ, the *Cristispira*, the *Borrelia*, and the *Leptospira*. The idea here presented is not a new one, for it seems that Schaudinn, before his untimely death in 1906, expressed the belief that his microorganism was, in actuality, a protozoön. McDonagh has been bold enough to describe a complete cycle of evolution on what is, perhaps, insufficient evidence. But numerous observers, following in the footsteps of Meïrowsky and Levaditi have demonstrated beyond any reasonable doubt that the *Treponema pallidum* does possess a granular stage. They have not, however, been able to show conclusively that these granules are virulent, and thus, that they are a portion of an evolutive cycle, though much of their work has been strongly suggestive. While it is, perhaps, unnecessary to state that nothing short of absolute proof of this evasive problem should be accepted, it would seem that further studies with slight modifications of the older techniques might bear worthwhile fruit.

Pemphigus Treatment With Partly Successful Results.—SULZBERGER and WISE (*Med. J. and Rec.*, 1932, 136, 64) report 5 consecutive cases of pemphigus, 3 of which were either cured or markedly improved, 1 died of pneumonia while apparently improving, and 1, after a complete remission, suffered a severe recurrence after an abdominal operation. The type of treatment suggested by the authors is as follows: (1) Expert nursing; (2) many local measures, including potassium permanganate baths, lotions, etc.; (3) large doses of arsenic; (4) daily high colonic irrigations with large quantities of fluid containing either bicarbonate of soda or an iodine preparation; (5) large quantities of vitamin D; (6) salt-poor, protein-low, vitamin-high diet; (7) trichophytin or monilia vaccine or both. No scientific basis for the above therapeutic measures is claimed by the authors, but empirically they seem to promise the best results as yet available.

GYNECOLOGY AND OBSTETRICS

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Statistics on Cancer of the Cervix.—The report presented by PHILIPP (*Zentralbl. f. Gynäk.*, 1932, 56, 212) from Stoeckel's Clinic in Berlin is based on 446 cases of cervical cancer which were treated between 1923 and 1925. Of this number 40.8 per cent were operable, 19 per cent were borderline and 40.2 per cent were inoperable. The rate of 5-year cures for the group as a whole was 36 per cent but by separate groups it was 57.3 per cent for the operable, 31.7 per cent for the borderline and 16 per cent for the inoperable cases. Of the entire group 131 cases were subjected to surgical operation and 74 (56.5 per cent) remained free from recurrence. Most of these operations were performed by Bumm and Warnekros, who preceded Stoeckel at this clinic. Of this series of operations 109 were in the operable class, with 62 per cent cures, 19 were borderline, with 31.5 per cent cures, and 3 cases were inoperable and all died. Irradiation was given in a series of 315 cases of whom 27.6 per cent remained free from recurrence. By groups this series consisted of 74 operable cases, with 50 per cent cures, 66 borderline, with 32 per cent cures, and 175 inoperable, with 16.6 per cent cures. A comparison of these results with those published from the same clinic for the years 1913–1919 shows that the rate of cure in the old series was 40 per cent for operation compared to the present 56.5 per cent and 15.25 per cent for irradiation as compared to 27.6 per cent in this series. The primary mortality in the 131 Wertheim operations was 8.4 per cent, of which only 5.3 per cent were due to infections. This low rate of fatal infections is probably due to the fact that virulence tests are performed on all carcinomas before operation and those cases which are infected with organisms of high virulence are excluded from operative treatment. Most of the operative cases received post-operative irradiation, but the author is not definitely prepared to say that it has improved the results. In 108 patients the regional lymphatic glands were examined and of 16 cases which showed carcinoma only 2 are free from recurrence as opposed to 58 free from recurrence in a series of 92 in which the glands showed no carcinomatous infiltration. Considering the results of irradiation it was found that the present series showed a curability rate of 50 per cent in operable cases, 32 per cent in borderline and 16.6 per cent in inoperable cases as against 28, 21 and 6 per cent for similar groups in the earlier series. The improvement in these results has been due to improved technique and not to any change in the type of material treated. No advantage was noted in the combination of radium and Roentgen ray over radium alone. A

comparison of the relative cures obtained by irradiation and by operation would seem to indicate that operation gives better results in the early operable cases, but in the borderline and inoperable cases irradiation seems preferable. While statistical summaries are usually very uninteresting, this report, coming from one of the foremost German clinics where there has been an extensive experience in both the operative and irradiation treatment of cervical cancer, shows that their results are excellent for this type of work and have materially improved since the previous report was published.

Cervical Polyps.—When a cervical polyp is found in the course of a gynecologic examination the usual feeling among gynecologists is that an entirely benign lesion is present and that the simple removal of the polyp is all that will be necessary for the complete cure of the patient. That such an opinion is not always justified is stated by FRANKL (*Zentralbl. f. Gynäk.*, 1932, 56, 1858), of Vienna. In a series of 318 cases he found a carcinoma of the cervix in the tissues adjacent to absolutely benign polyps in 3 instances. Such an experience, he believes, emphasizes the necessity of careful palpation and inspection of the cervix together with exploration of the cervical mucosa with a sound and when broken particles of tissue are recovered, microscopic examination of such tissues. In the presence of a frankly carcinomatous cervical polyp even without associated carcinoma of the cervix, he believes that panhysterectomy is indicated. (The pedicle of the polyp should be examined with especial care.—C.C.N.)

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Uveitis With Dysacusia, Alopecia and Poliosis.—Three cases of severe uveitis resulting in secondary glaucoma, phthisis bulbi, or both, and associated with transitory deafness, alopecia and depigmentation of the skin and hair, particularly of the eyebrows and eyelashes, is reported by RONES (*Arch. Ophth.*, 1932, vol. 7). In none of these cases was any specific cause of the uveitis found. One of the patients was found to be sensitive to uveal pigment. The fundus was not visible in any of the 3 patients reported by the author. But in several previously reported similar cases depigmentation of the choroid was observed. Depigmentation of the hair and also deafness and alopecia have been reported in association with sympathetic ophthalmia. This fact, taken in connection with the proven sensitivity to uveal pigment in 1 of his cases, suggests to the author that the depigmentation of the

skin and hair seen in patients with inflammatory diseases of the uveal tract is not a chance association, but the result of an anaphylactic reaction affecting the pigmented tissues. These patients have a transient allergy to pigment. No evidence of endocrine dysfunction was found in the reported cases.

Hemorrhagic Retinitis in Vomiting of Pregnancy.—STANDER (*Surg., Gynec. and Obst.*, 1932, 54, 129) reports 2 cases of hemorrhagic retinitis occurring in patients with pernicious vomiting of pregnancy. The first patient was 5 months pregnant and had been vomiting and losing weight for 2 months. Numerous retinal and subhyaloid hemorrhages of varying size were present in each eye without arterial changes, exudates or edema. Therapeutic abortion was performed 8 days after the onset of hemorrhages, but the patient died 1 day later. Necropsy revealed central necrosis of the liver and numerous patches of necrosis with many hyalin capillary thrombi in the anterior lobe of the hypophysis. The second patient was 4 months pregnant and had been vomiting severely and had lost 30 pounds. Many subhyaloid hemorrhages were present in each eye. Therapeutic abortion was performed immediately after the discovery of the hemorrhages. The patient recovered and most of the hemorrhages had disappeared 3 weeks later at the time of her discharge from the hospital. The changes in the blood and urine in these patients were of the type seen in severe vomiting of pregnancy. No hypertension was present. The hyperglycemia in the first case may have been caused by the lesions in the hypophysis. The hemorrhages in the retina were apparently due to toxic injury to or increase in permeability of the capillary walls. The occurrence of such hemorrhages in the course of vomiting of pregnancy should be regarded as a grave prognostic sign and as an absolute indication for immediate termination of the pregnancy.

Some Remarks on Changes of the Eyeground in Toxemia of Pregnancy.—PILLAT (*Chinese Med. J.*, 1932, 46, 149) discusses the occurrence of "retinitis of chronic nephritis in pregnancy" and of "retinitis in toxemia of pregnancy." He believes that it is impossible to distinguish the two ophthalmoscopically with any degree of certainty since the picture of each is made up of edema, hemorrhages, punctate exudates, star figures, cotton-wool patches and vascular changes. Four points favor the diagnosis of retinitis in toxemia of pregnancy: The presence of "glassy" edema of the retina, the visibility of folds of the membrana limitans interna, the absence of a typical star figure, the tendency to detachment of the retina. This type of retinitis usually occurs in the last three months of pregnancy with rather sudden onset and heals rather rapidly after the birth of the child. It seldom recurs in subsequent pregnancies. Retinitis of chronic nephritis in pregnancy is apt to occur earlier in the course of the pregnancy, to be chronic and to recur in succeeding pregnancies. The author does not believe that it is necessary to assume a special pregnancy toxin to account for the occurrence of retinitis in pregnancy. Aside from the presence of a recognizable chronic nephritis, it is possible for the woman to have

latent primary or toxogenous hypertension with some damage to the vessel walls which is not recognized by our ordinary tests unless perhaps by examination of the retinal vessels. The strain imposed on these damaged vessels by an ordinary pregnancy might be sufficient to cause lesions of the brain, kidney and retina. Until such latent vessel lesions can be definitely ruled out in all cases, we are not justified in assuming the existence of a retinitis due to circulating pregnancy toxins. The author thinks that optic neuritis and retrobulbar neuritis occurring in the course of pregnancy but not in association with retinitis are due not to the pregnancy proper but to some exogenous factor.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Symptom of Acute Suppurative Sphenoidal Sinusitis Not Previously Described.—MENZEL (*Monatschr. f. Ohrenh.*, 1932, 66, 81) reports 4 cases of acute sphenoiditis in which lacrimation was a prominent symptom. This is a result of excitation of regional nerves—directly or indirectly—by the inflammatory process in the sphenoid sinus. Menzel urges that widespread observations be made in order to determine more accurately the actual incidence of lacrimation in sphenoiditis.

Pathologic Changes in the Auditory Nerve in Otosclerosis and Their Significance Clinically, Especially With Regard to Paracusis Willisii.—Based upon a histopathologic study of the auditory nerves from four subjects who had suffered from otosclerosis during their life. GRAY (*J. Laryngol. and Otol.*, 1932, 47, 598) reports many interesting observations and enlightening conclusions: In otosclerosis, the degenerative process begins in the medullary sheath and neurilemma of the cochlear nerve, and later in its axis-cylinder. This process occurs independently of the stapedial fixation or of the bony changes in the labyrinthian capsule—and it probably precedes both. The clinical picture of otosclerosis—deafness, paracusis Willisii and tinnitus—is produced for the most part by cochlear nerve degeneration and later only to a minor degree by fixation of the stapes. Gray believes that the diminished secretion of wax in the meatus, the sluggish vasomotor reaction and accompanying diminished sensitiveness of the tympanic membrane, the osseous change in the labyrinth and the degeneration of the cochlear nerve fibers are independent resultants of a common etiologic factor, which is probably to be looked for in the vasomotor arc that controls the nutrition of the structures involved. Incidentally, he thinks that atrophic rhinitis is due to a defective vasomotor mechanism of the nasal reflex arcs.

RADIOLOGY

UNDER THE CHARGE OF

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ROCHESTER, MINN.**The Roentgen Ray Treatment of Gonorrheal Complications in Males.**

—Deep Roentgen ray therapy in the treatment of the various complications of gonorrhea was studied by LIBERSON (*Radiology*, 1932, 18, 758) in 119 males over a period of $6\frac{1}{2}$ years. In the order of efficacy, Roentgen ray therapy appears to be uniformly effective in painful heel due to a periosteal spur, may relieve pain of gonorrheal joint complications and has little effect on epididymitis, adenitis or urethritis.

Roentgen Therapy in Bone Metastasis of Carcinoma.—Most of the patients treated by STENSTROM (*Radiology*, 1932, 18, 741), particularly those exhibiting the osteoclastic type of metastasis, were benefited. Although the improvement was of rather short duration for the group as a whole, it was quite remarkable in some few instances. The Roentgen treatments seemed to be of very definite value in reducing the amount of drugs needed for pain, in getting patients out of bed and in restoring some of them to useful lives for as long as 2 years.

An Original Method of Estimating Kidney Function by Means of the Roentgen Ray in Intravenous Urography.—CARHART (*Am. J. Roent. and Rad. Ther.*, 1932, 27, 234) has devised a rapid method of estimating the percentage of skiodan eliminated in 30 minutes, and hopes that this will prove to be a direct test of renal function. Six flat-bottom, 20-cc. test tubes are grouped around a similar one at the center. Fifteen cubic centimeters of 2, 3, 4, 5, 6 and 8 per cent solutions of skiodan, respectively, are placed in the outer tubes, forming a scale or meter. In the central tube of the meter is placed 15 cc. of skiodan urine voided by the patient 30 minutes after the intravenous injection. A roentgenogram of the assembled tubes is then made, and the density of the central tube is compared with that of the scale tubes containing the known percentages of skiodan. The quantity of urine passed at 30 minutes is also measured. With these data simple mathematical calculation will determine the total excretion of skiodan in 30 minutes. It is considered that approximately 40 per cent of the skiodan injected should be eliminated at 30 minutes. To be sure that there is no residual urine in the bladder a film is exposed over the bladder area after collecting the 30-minute specimen.

Roentgen Treatment of Agranulocytosis.—Two cases of agranulocytosis successfully treated by Roentgen irradiation are reported by GAGER and SPEER (*Am. J. Roent. and Rad. Ther.*, 1932, 27, 40). Both cases occurred in young women. In the first case one-third of an

erythema dose applied to the femur produced an immediate amelioration, but several subsequent applications were required for clinical cure. In the second case a single application brought prompt and lasting improvement. The writers consider these results to be an unequivocal demonstration of the specific value of Roentgen irradiation in stimulating the production of granulocytes and of the vital importance of these cells to the body.

Hepatosplenography.—To produce readily visible shadows of the liver and spleen, KADRKA (*Radiology*, 1932, 18, 371) has employed thorotrast, which is a 25 per cent solution of thorium dioxide. For intravenous use it is diluted at least 10 times with 5 per cent glucose solution, sterilized by heating, and injected in increasing doses in the course of several days. To determine the patient's tolerance an initial dose of not more than 0.1 grain of thorotrast per kilogram of body weight is given. "After that each dose is increased from 0.1 to 0.5 grain per kilogram of body weight until the desired dose is given, care being taken not to exceed the patient's tolerance." As a rule, a total of 0.8 grain is sufficient to produce an intense shadow. Roentgen observation should be made 24 hours after the last injection. The injections are generally well borne, and the method has appeared harmless over a limited time. "Until it has been used in a larger series of cases, and these have been observed for a longer period of time, it should not be used routinely, especially in young individuals. The indications at present are limited to cases of carcinoma, echinococcus cysts and abscess of the liver and spleen, especially those in which there is a likelihood of subsequent surgical interference." The method should not be used in patients with severe hepatic or splenic insufficiency, especially those in whom there is also renal damage. Excretion of thorotrast is very slow and only after several months is there an appreciable diminution of the shadow density.

A Demonstration of the Lymphatic Drainage From the Maxillary Sinuses.—Ten weeks after injection of a maxillary sinus with lipiodol a roentgenologic examination of the patient was made by PFÄHLER (*Am. J. Roent. and Rad. Ther.*, 1932, 27, 352). At this time a globule of lipiodol was retained in the sinus and there were scattered deposits in lymph spaces from the zygoma to the clavicle, including the submental and sublingual regions. Films made 1 year later showed relatively little change in distribution but some general reduction. The author considered the case interesting in showing that upward drainage occurs, that lipiodol does not accumulate in the lymph nodes and that elimination of the drug by absorption may be extremely slow.

Giant-cell Bone Tumor.—PEIRCE (*Am. J. Roent. and Rad. Therap.*, 1932, 28, 167) reports the results of treatment in 14 cases. In his opinion, Roentgen irradiation in repeated and relatively moderate doses offers the most for the patient, except when for cosmetic or functional reasons better results can be obtained by the addition of surgical intervention; but this should not follow Roentgen therapy short of 6 weeks or more. If surgery is contemplated thorough chemical cauterization of the cavity should be executed, followed immediately by a consistent program of Roentgen therapy.

NEUROLOGY AND PSYCHIATRY

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A Contribution to the Study of Truancy.—BROADWIN (*Am. J. Orthopsychiat.*, 1932, 3, 253) states that truancy is to be considered merely as one aspect of the total personality in its adjustment or maladjustment to the total situation. The study of the problem of truancy may open to us important personality disorder which might otherwise go unsuspected. It requires a study of the child and his unconscious psychic life, his instinctual strivings, their evolution and forms of expression. There are many generally accredited reasons for truancy, as loss of interest because of backwardness, bad associates, and so forth. Reasons of such character do not express the problem in terms of the deeper personality factors. "Since the school situation is in many respects a substitute for the situation in the home, one must seek a relationship between the adjustment in the home and the adjustment in the school. Truancy from school may then have its correlation in behavior symptoms in the home. It may represent an act of defiance, an attempt to obtain love, or escape from real situations to which it is difficult to adjust." This article describes a form of truancy occurring in the child who is suffering from a deep-seated neurosis of the obsessional type or who displays a neurotic character of the obsessional type. The truancy is part of the general symptomatology and part of the multiplicity of personality difficulties which have received little corrective attention. In the typical case the child is absent for periods varying for several months to a year. The parent knows where the child is, that is, hear the mother or home. The truancy is not understood by the parents or school. The child may say that it is afraid to go to school, afraid of the teacher, or says it does not know why it won't go to school. At home it is happy and carefree; at school it is fearful, miserable and runs away at the first chance. In the course of treatment the child eventually feels free to discuss problems. Obsessive ideas are revealed, such as the death of the mother or that the house is on fire, and so forth. The child feels that he must run home. Then he fears the return to school because of "terrible feeling" when these ideas come to his head. He would not tell these ideas before because they are "crazy ideas" and people might think him "crazy." The reasons obtained from the child are meaningful in that they indicate the strong infantile love attachment to the mother and the intensive sadistic or hostile attitude towards her, which underlie the anxiety. "There is conflict between the primitive instinctual drives which demand expression and the ego . . . The symptom implies a gratification of the prohibited instinctual drives and at the same time contains the elements

of self-punishment to mollify the super ego. The punishment is expressed as the anxiety or the disability borne by the patient." Two typical cases are presented and discussed in a moderate amount of detail. Conclusions are that the understanding and treatment of these cases and other cases of truancy "can most effectively be approached through the handling of the unconscious psychic life of the patient, the evolution of the love and hate instincts. It is in the light of this that one can feel that the best results would be obtained from classical child analysis. However, we all know that at present such a procedure is not practicable in child guidance clinics. One then must employ a modified form of approach. Although one can feel that an improvement is brought about, the question remains open as to whether deep inroads are made on the basic neurosis by the clinic procedure."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Osteitis Fibrosa.—A short review of the earlier and more recent work on osteitis fibrosa together with conclusions of original studies have been reported by LAND (*Am. J. Path.*, 1932, 8, 263). Attention is called to the observations of Pommer who regarded cyst formation dependent upon hemorrhage following trauma. The resulting congestion and inflammatory response along with chronic irritation produced by functional activity leads to a resorption and atrophy of the surrounding bone, a sclerosing process in the marrow, and the formation of new bone with secondary hemorrhage and progressive cyst formation. This is most commonly seen following injury to the epiphysis in the young, the hemorrhage and edema remaining localized if the periosteum is still intact. The resorptive and sclerosing process is compared to the induration in parenchymatous organs following chronic passive congestion, similar changes also being seen in callus formation, secondary new growths and tuberculous and syphilitic bone lesions. Studies concerning the relationship between osteomalacia, osteitis fibrosa and rickets reveal that those parts of the skeleton most subject to strain yield because of insufficient calcification. In these conditions congestion of the blood and lymph vessels, with continuous mechanical irritation, may lead to osteitis fibrosa. The recent experimental production of this lesion by Jaffe, Bodansky and Blair through the administration of parathormone, and the occasional association of osteitis fibrosa with hyperplasia or tumors of the parathyroid glands do not invalidate the above conception, the vascular disturbances being secondary to the action of functional trauma on softened bone.

The Pathology of Aneurysm: A Review of 167 Autopsies.—GARLAND (*J. Path. and Bact.*, 1932, 35, 333) makes a statistical study of the cases of aneurysm occurring in 12,000 autopsies at the Leeds General Infirmary and the findings are compared with similar studies in the literature. One or more aneurysms were found in 167 cases. Aneurysm of the thoracic aorta was found in 78 cases; 7 cases showed 2 aneurysms and 1 case 3, making a total of 87 thoracic aortic aneurysms. Aneurysm of the ascending aorta was the most common and was present in 34 cases. The corrected ratio of incidence for males and females was 1.75 to 1. Saccular aneurysms were the most common type encountered. The majority of the aneurysms were syphilitic in origin. Two appeared to be atheromatous and 2 were infective. Thirty-three per cent ruptured into the pericardium. Four cases of aneurysm of the sinuses of Valsalva were found, 2 being mycotic and 2 syphilitic. The average age for thoracic aortic aneurysms coming to autopsy was 53 years. Death was due to rupture of the aneurysm in 36 cases, to pressure effects in 27 and unrelated to the aneurysm in 18. Sixteen cases of abdominal aortic aneurysm were encountered, 7 were syphilitic and 9 atheromatous. The average age at autopsy was 65 years. There were 32 cases of cerebral aneurysm. The author points out that many cerebral aneurysms are probably missed. Death resulted from rupture of the aneurysm in 84.3 per cent of the cases. Most of the aneurysms were smaller than a pea. The most common site was the right middle cerebral artery, where 10 aneurysms were situated. Fourteen aneurysms were associated with gross arterial disease, usually atheroma, and 5 were syphilitic. Only 1 aneurysm of the "miliary" type was found and that was in an advanced arteriopathy. There were 28 cases of aneurysms of the heart, 21 of which were in the left ventricle. In 1 case there was a minute aneurysm of the right coronary artery associated with atheroma. Four cases showed aneurysm of the mitral or aortic valves associated with endocarditis. Of the small vessels aneurysms of the splenic artery were the most numerous after the cerebral arteries. Five cases were found all due to atheroma. Three cases of renal aneurysm were found, 2 of which were probably syphilitic. The rarity of renal aneurysm is stressed. Twelve cases of peripheral aneurysms were syphilitic, mycotic, atheromatous or traumatic. In summing up the causes of aneurysm the author considers that the large proportion of cerebral aneurysms in the first half of life are congenital in origin. Trauma was found to be a rare cause of aneurysm. Syphilis was found to be the most important single cause of aneurysm, producing 91.3 per cent of thoracic aortic aneurysms. Embolism as a cause of aneurysm was almost always associated with infectious processes, the most common infection being infective endocarditis. In many cases no vascular abnormality but atheroma was found as a cause of aneurysm. Atheroma was also found in association with other abnormalities as a contributory cause of aneurysm.

The Occurrence of True Bone Within a Renal Calculus.—STUART and KRIKORIAN (*J. Path. and Bact.*, 1932, 35, 373) report the occurrence of true bone within a renal calculus. Several stones were evacuated at operation from the kidney of a female, aged 22 years, who had a definite history of pyelitis and nephrolithiasis for at least 6 years.

Six stones were examined. The stones contained 70 to 80 per cent calcium oxalate and 6 per cent calcium phosphate. Five of the stones showed nothing unusual. The sixth stone was bilobed and was the shape of an acorn. A tag of fibrous tissue was seen entering a small foramen at the junction of the two lobes of the stone. The tag of tissue was evidently a pedicle torn from its attachment to the kidney pelvis. Section of the stone revealed a central cavity filled with a gritty white substance from which blood exuded. On microscopic section the central core was found to consist of compact and cancellated osseous tissue as well as a periosteum-like membrane adjacent to the compact portion. Numerous capillaries and spaces for fat and marrow tissue were also seen. The rarity of the condition is emphasized and 2 similar cases reported by PHEMISTER (*Ann. Surg.*, 1923, 77, 135), the only cases to be found in the literature, are quoted. In explaining the vicarious osteogenesis reference is made chiefly to the work of HUGGINS (*Arch. Surg.*, 1931, 22, 377), who showed a clear relationship between proliferating epithelium in the kidney pelvis of dogs and the formation of bone in the mucosal stroma. The theory is postulated that infection in the kidney pelvis leads to the proliferation of epithelial buds and that bone formation begins in the fibrous core of such buds. Continuation of the process leads to a greater formation of bone and the eventual erosion of the covering epithelium. The bone then connected by a fibrous pedicle to the kidney tissue forms a nidus for the deposition of calcium salts from the urine. ———

The Interstitial Reactions Caused by Various Dusts and Their Influence on Tuberculous Infections.—KETTLER (*J. Path. and Bact.*, 1932, 35, 395) injected 0.5 to 1 cc. of 1 to 3 per cent suspensions of various silicious and nonsilicious dusts into the flanks of a series of mice. The animals were killed at varying intervals and sections were made of the local lesion. The characteristic feature of the lesions produced by nonsilicious dusts was their quiescence. There was only a slight transient cellular reaction. Amorphous, colloidal and crystalline silica, mine dust containing silica, shale, kaolin and asbestos, all produced a local coagulative necrosis accompanied by a marked cellular reaction. Carborundum, a silicious dust, and silica encrusted with iron oxid were inert and produced a lesion similar to the nonsilicious dusts. In order to test the effect of the dusts upon a tuberculous infection a batch of mice were inoculated into the right and left flanks with suspensions of two of the dusts to be tested, and after an interval (usually 24 hours) an emulsion of living tubercle bacilli was injected into the general circulation by way of the tail vein. The mice tolerated heavy doses of the bacilli, and 0.33 to 0.5 cc. of an emulsion containing 500,000 bacilli per cc. was used. The animals were killed at varying intervals and the general bodily seeding of bacilli and the numbers of bacilli in the dust-produced lesions were estimated by stained sections. The distribution of the organisms throughout the body was satisfactorily constant. An occasional mouse showed an unduly heavy seeding and had to be discarded. It was found that the inert or nonsilicious dusts had a neutral effect on the progress of the interstitial tuberculous lesions, while the active or silicious dusts with the exception of carborundum and silica coated with ferric oxid had a positive influence.

The numbers of bacilli varied greatly from lesion to lesion, but there was a great preponderance of organisms in the active silicious lesions. The present methods of producing pneumoconiosis in laboratory animals, by exposing them to dusty atmospheres, is too laborious and takes too long—2 years or more—to be of great practical value. The author suggests the injections of suspensions of dust into the interstitial tissues as a useful and dependable method for the determination of the pathogenicity of atmospheric pollutions in various industries.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Etiology of Dental Caries.—There are, in general, two conflicting views in regard to the etiology of caries of the deciduous as well as of the permanent teeth. The one, older and better entrenched, holds that dental caries is due mainly to local conditions, to peculiar configurations of the occlusal surface or to an abnormal environment within the mouth which invites decay. The other view is that caries is essentially a systemic disturbance and that local factors are of secondary significance. HESS and ABRAMSON (*Dental Cosmos*, 1931, 73, 849) report the results of the examination of two groups of children who had been closely observed during infancy (some 6 or 7 years ago). One group was known to have been free from rickets and the other to have had the disease in mild or moderate form during the first year of life. It was found that the children who had been protected from rickets had developed less caries than those who had not been protected. Nevertheless, numerous instances of dental caries were found in the nonrachitic group. The deciduous teeth as well as the first molars were involved. Considerable caries was likewise observed in the teeth of a group of children who had been breast-fed and had shown no evidence of rickets in a study carried out in 1922 and 1924. An average degree of caries was found in the teeth of children whose mothers were given cod-liver oil during the latter months of pregnancy; this group likewise had been studied for rickets about 7 years ago. A consideration of the geographic distribution of dental caries brought about the fact that it is rampant among the children and adults in the subtropics and tropics, for example, in Florida, Hawaii, Jamaica and Trinidad. This distribution constitutes a strong argument against regarding rickets as the essential etiologic factor of dental caries. A similar consideration of geographic distribution argues against the acceptance of scurvy as

an important causal factor of caries, which is present in marked degree where fruit and vegetables are in greatest abundance and, on the other hand, is least prevalent in countries, such as Alaska and Greenland, where antiscorbutic foods are scarce. An analysis of clinical conditions likewise indicates that dental caries cannot be attributed to a deficiency of vitamins A or B. Pathologic lesions of the enamel are by no means infrequent among young children. This is a disorder quite distinct from caries and involves particularly the upper incisor teeth. It is found in the deciduous teeth of children who have had neither rickets nor scurvy. As has been shown by others, there is often an association between this disorder, infantile tetany and a deficiency of calcium in the blood. A relationship exists between the growth and the occurrence of caries and more particularly between development and caries. This is clearly brought out by plotting a curve of incidence of caries and noting the exceptionally high incidence at the period of adolescence and the years immediately succeeding.

Diphtheria Antibodies Transmitted from Mother to Child.—NEILL and coworkers (*J. Immunol.*, 1932, 22, 117) made measurements of the diphtheria antibodies in the blood of a mother and baby during the 18 months following the birth. Tests were made for antibodies of the antibacterial sort as well as for the antitoxin. The antibacterial antibodies were found in the serum of the baby over the period in which placentally transmitted antibodies could be expected to be retained, but owing to their passive origin they were absent in later bleedings. Control tests showed that the antibacterial antibodies were absent in the sera of babies whose mothers did not possess them. The data of the antitoxin tests owe their interest to the high degree of immunity of the mother and to the length of time over which the blood of both baby and mother was studied.

The Relation of Bovine Mastitis to Human Infection.—BROOKS (*J. Prev. Med.*, 1932, 6, 111) points out that mastitis is common among dairy cattle and the infection is readily communicated from one cow to another. The types of streptococci which are the common incitants apparently are not infective for man, but when present in milk in large numbers with their toxins may be responsible for severe toxic disturbances, especially in children. Organisms of animal or human origin, pathogenic for man, may be present in diseased udders. These include the tubercle bacillus, *Brucella abortus*, and the hemolytic streptococci which are incitants of septic sore throat and scarlet fever. Udders infected with *Brucella abortus* may excrete the organisms during the life of the animal. Agglutination and complement-fixation tests on milk from infected quarters have given positive results, that from uninfected quarters negative. Agglutinating power in the blood may be due to infection localized in the udder. Several milk-borne epidemics of septic sore throat in upper New York State have been traced to raw milk from herds with cases of mastitis. In the more recent epidemics hemolytic streptococci corresponding to those found in the human cases have been obtained from the infected udders. Recent experience suggests the desirability of persistent effort to find the infected cows. One epidemic of scarlet fever in 1922 was traced to

raw milk, including that from a cow with mastitis from which hemolytic streptococci were obtained. Experience suggests that organisms from human sources are primarily responsible. Since January 1, 1924, 6 outbreaks of gastroenteritis have been traced to raw milk from herds in which there were cases of mastitis. In 3 of these most of the patients were children given the milk in school. Illness developed within 4 or 5 hours. Cows with chronic mastitis were involved and common types of nonhemolytic streptococci isolated. Bovine mastitis is a major problem in prevention of milk-borne infection. A slowly developing movement for eradication offers no practical and immediate solution, nor will careful dairying methods and inspection afford adequate protection. Pasteurization is the only practical safeguard.

A Study of Certain Epidemiologic Factors in the Pneumonia of Children.—SHULTZ (*Am. J. Hyg.*, 1932, 15, 80) determined the incidence of pneumococcus carriers by cultures from the throats of 86 individuals, representing the families of 21 children with pneumococcus pneumonia. In 11 carriers, or 12.7 per cent, of those studied, the type of pneumococcus found was the same as that isolated from the pneumonia patient. The virulence of the pneumococcus from several cases was compared with the virulence of the strains isolated from the corresponding carriers. There was no significant variation. The virulence of Type I organisms obtained from cases and carriers was higher than the virulence of Types III or V isolated from the cases. The duration of carrier state was followed in 35 convalescent children and was found to vary between 2 and 152 days. Types I and III remained in the pharynx for a longer period of time than Type II or the subdivisions of Group IV. The pneumococci found to replace the infecting types did not differ greatly from those found in the pharynx of the healthy contact. The unclassified pneumococcus which apparently replaced the infecting type might in some instances have been a degraded form of the original strain. Two children who developed symptoms of pneumonia in the hospital were studied from the viewpoint of ward infection. The sources of the infections could not be traced. The author concludes that until further study increases our knowledge of the factors involved in the etiology of pneumonia, preventive measures can only be directed toward the epidemiologic control of the suspected modes of transmission in children—healthy carriers and convalescent patients.

Milk-borne Septic Sore Throat and Scarlet Fever and Their Relation to Beta Hemolytic Streptococci.—WILLIAMS and GURLEY (*J. Bacteriol.*, 1932, 23, 241) give a short review of the present status of "*Streptococcus epidemicus*" as a species and present evidence to show that neither of the characteristics claimed as the only species characteristics—capsule formation and moist growth on blood media—holds sufficiently to be used in designating a species and that at present strains of hemolytic streptococcus from septic sore throat not otherwise placed by agglutinin absorption should be termed simply *Streptococcus hemolyticus*. Strains of hemolytic streptococci from milk-borne epidemics of scarlet fever and of septic sore throat and from other sources have been studied to determine their serologic relationship to our type strains from scarlet fever and erysipelas and to each other. The strains from septic sore

throat in the 3 Massachusetts outbreaks of 1928 were shown to fall by agglutinin absorption partly into the largest scarlet fever group Type I and Subtype I and partly into 2 other groups. These 2 newly discovered agglutinative groups have been called epidemic (or septic sore throat) Type I and epidemic (or septic sore throat) Type II. Septic sore throat strains and scarlet fever strains may occur in the same epidemic, composed of cases classed mostly as scarlet fever. A scarlet fever type of organism may be recovered from cases recorded clinically as constituting a septic sore throat outbreak. Exotoxins of similar quality as regards their neutralization ability, but of varying quantity, have been produced by all of these type strains. The authors conclude from their studies that milk-borne epidemics of septic sore throat and of scarlet fever may be caused, respectively, by one or several agglutinative types of hemolytic streptococci. When scarlet fever predominates, usually the epidemic strain belongs to one of the common scarlet fever agglutinative types; when septic sore throat predominates, the epidemic strain may be one of several agglutinative types, respectively, 2 of which have been demonstrated in these studies and have been called tentatively epidemic agglutinative Type I and epidemic agglutinative Type II.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 21, 1932

Some Effects of Alpha Radiation on Cells.—R. E. ZIRKLE (Botanical Laboratory, University of Missouri). The properties of α rays make possible a great simplification of the system in the study of the effects of ionizing radiation on living cells. Polonium was used as source of α rays because it emits other rays to no significant degree and because of its convenience. Spores of the fern *Pteris longifolia* were irradiated because they can be handled in the air-dry condition and do not require aseptic culture methods. Three distinct processes connected with germination—cracking of wall, development of chlorophyll and cell division—are inhibited by α rays. The susceptibility of these processes increases in the order named. The doses required to produce 50 per cent inhibition of these processes are, respectively, 4000, 13,000 and 33,000 α particles per protoplast. These doses correspond to energy of the order 10^{-6} ergs per μ^3 absorbed by the protoplast. This is of the order of $\frac{1}{10}$ the energy per μ^3 calculated by others for 50 per cent inhibition of cell division in yeast. When a dose capable of producing 50 per cent inhibition of division is used, from 7 to 16 per cent of the protoplast is liable to direct alteration by ionization. When a dose capable of producing 50 per cent cracking is used, more than half and possibly all of the protoplast is liable to such direct alteration. Irradiation of definite fractions of the protoplast indicates the following conclusions: (a) Cracking, greening and division may each be inhibited

by extranuclear injury, but all are much more easily inhibited if the nucleus is irradiated. (b) The extranuclear injury which inhibits greening is not direct injury to plastids or proplastids. (c) Imbibition is inadequate for production of cracking in the normal spore. (d) Nuclear injury is a function of energy absorbed rather than of number of incident α particles.

A Study of the Influence of Electric Current Upon Nerves Growing in Tissue Culture.—S. C. WILLIAMS (Laboratory of Anatomy, University of Pennsylvania). Nerve cells and fibers from pieces of brain from 4- to 8-day incubated chick embryos cultivated *in vitro* in Tyrode-diluted chicken blood plasma with added embryonic extract were placed by means of a micromanipulator between silver-silver chlorid-Ringer-Ringer agar microelectrodes in a warm moist chamber. Electric current, of density 130 to 0.2 milliampere per square millimeter of average cross-sectional area of the tip of the electrodes, was applied for periods up to 20 minutes. Observations on more than 100 experiments show a formation of granules in the cytoplasm, a softening and retraction from the cathode with occasional formation of short temporary pseudopodia and generally a movement toward the anode. Strong current is quickly lethal; weaker current is now being used and its effects over longer periods of time studied. This work was done in part in collaboration with Dr. T. Petérfi at the Kaiser-Wilhelm Institut für Biologie in Berlin, and with the assistance of a grant from the Faculty Research Committee of the University of Pennsylvania.

The Anion Cation Content of Normal and Infected Gall Bladder Bile.—C. G. JOHNSTON, I. S. RAVDIN, C. RIEGEL and J. H. AUSTIN (Laboratories of Surgical Research and Research Medicine, University of Pennsylvania). We have previously reported the anion cation concentrations of certain constituents in normal dog's hepatic and gall bladder bile. When the gall bladder is normal it alters hepatic bile by concentrating the calcium, bile salt and base. The chlorid and total CO_2 concentrations decrease and the pH is reduced. Fluid is always absorbed. When the gall bladder becomes damaged fluid pours into the gall bladder. Base remains as in hepatic bile, while bile salts and calcium decrease in concentration and chlorid and total CO_2 increase in concentration. The pH is increased. Normal human gall bladder bile is similar to normal dog gall bladder bile in its concentrations of the substances studied. Studies of human bile removed from the diseased gall bladder at operation have now been made. Changes similar to those obtained in the dog when the gall bladder is infected have been observed. Roughly the data from the diseased gall bladder are divisible into 3 groups on the basis of chemical analyses and the ability of the gall bladder to concentrate its contents as evidenced after the administration of sodium tetraiodophenolphthalein. With increasing damage there is a tendency for a reduction of bile salts and calcium and an increase in chlorid and total CO_2 concentrations, until in the nonvisualized gall bladder containing stones bile salts, as demonstrated by the Gregory-Pascoc reaction, are frequently absent, while chlorid is above the blood level and calcium is present in approximately the same concentration as found in hepatic bile. Between normal human

gall bladder bile and that found in the severely damaged gall bladder one finds bile in which the bile salt concentration decreases with increasing histologic evidence of disease.

The Colorimetric Estimation of Chlorids in Blood and Urine.—B. B. WESTFALL (Laboratory of Pharmacology, University of Pennsylvania). When silver chromate is suspended in an alkali chlorid solution silver chlorid and alkali chromate are formed in stoichiometric proportions. The concentration of chlorid in a solution can therefore be determined by adding powdered silver chromate, stirring, filtering and estimating the liberated chromate in the filtrate. Estimation of chromate can be accomplished with great accuracy by mixing with Cazeneuve's reagent (s-diphenylcarbazon) whereupon an intense purple-red color is produced. The color production follows Beer's law over a satisfactory range. Standard sodium chlorid solutions or standard sodium chromate solutions may be used for the production of standard colors with which comparison is made. The color produced is so intense that very small amounts of chlorid can be estimated.

A micro modification of the method was described by which it is possible to determine the chlorid content of 0.0001 cc. containing as little as 0.0004 mg. sodium chlorid, with an average error of about 3 per cent.

The Chlorid Content of Glomerular Urine and Plasma From Frogs.—B. B. WESTFALL and A. N. RICHARDS (Laboratory of Pharmacology, University of Pennsylvania). In a series of 11 consecutive experiments glomerular urine and blood plasma were collected from normal frogs and analyzed for chlorid by the method described above. The greatest difference found in chlorid content of the 2 fluids was 6 per cent; the average difference was less than 2 per cent. The conclusion is that in respect of chlorid, glomerular urine in frogs is an ultrafiltrate from plasma.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

FEBRUARY, 1933

ORIGINAL ARTICLES.

MERCURY POISONING.

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THE evaluation through clinical results of any measures employed for the treatment of mercury poisoning is extremely difficult, chiefly because estimation of the effective doses of mercury is almost impossible. In all series of cases recoveries are reported after enormous doses, death after comparatively trivial amounts of the drug. In dogs Sansum²⁷ found that 4 mg. of the bichlorid given intravenously proved almost regularly fatal, although it did not produce anuria; 5 mg. per kilo invariably caused anuria and death. Such doses, equivalent to only 0.28 to 0.35 gm. for a 70-kilo human are far smaller than those which have proved lethal in clinical studies of poisoning. Haskell, Carder and Coffindaffer¹⁰ administered the drug in solution by stomach tube to dogs who had received an injection of morphin to allay the tendency to vomit. Under these circumstances they found that a dose of 20 mg. per kilo was invariably fatal. The extraordinary difference in magnitude between the intravenous and peroral minimal lethal doses can be ascribed to incomplete or retarded absorption from the alimentary canal. If the tolerance of humans is similar to that of dogs, it would be a reasonable expectation that a 70-kilo adult would survive if he took and retained less than 1.4 gm. of the drug. In

other words, recovery after the ingestion of less than 3 of the common 7.5-grain tablets should be considered imperfect evidence of therapeutic success. This conclusion is in accord with most clinical reports, including the series of cases which will be presented below.^{1,9,29}

The situation is still further complicated in human cases by the early institution of measures to prevent absorption and to recover the drug from the stomach before it can be absorbed. The outcome of bichlorid poisoning is largely dependent upon the interval which elapses between the ingestion of the mercury and the institution of emetic measures and gastric lavage.^{1,9,29}

It is not entirely possible to resolve these doubts by quantitative analysis of the excreta. The analytical difficulties involved in the quantitative recovery of mercury from the enormous mass of fluids used for lavage or excreted in diarrhea and vomiting are considerable. Early vomitus, urine, stools and lavage fluids are invariably incompletely preserved. Moreover, in the initial stages, at least, it is hard to know whether to count mercury recovered from the bowel and stomach as part of the effective dose or merely unabsorbed material.

For all these reasons mortality statistics afford an extremely uncertain criterion of the value of any therapeutic measures. Certain data on the cases treated in the New Haven Hospital, from 1922 to the present, are, however, worthy of mention.

In all, there have been 37 patients who presumably took mercury in the form of bichlorid tablets. One of these is supposed to have attempted suicide by this means twice. Of the 37, 28 survived, 9 died, a mortality of approximately 25 per cent. Of the survivors, in spite of history and circumstantial evidence, there is some uncertainty whether 4 patients took or absorbed any significant amount of poison. Cases have been omitted whose histories of poisoning seem entirely unreliable. As far as the relation of dosage of mercury and initial treatment to mortality is concerned, the results in this series differ little from those reported by other observers. No patient who had received less than 3 tablets of bichlorid (1.5 gm.) died; none who had taken more than 4 tablets survived. Of the 6 who survived after taking 3 or 4 tablets, 1 spit out 2 of the 3 tablets unswallowed; 1 was reported to have taken 4 tablets in solution, but no mercury was found in his urine. One other survivor is known to have taken more than 1 tablet, but the actual amount taken is uncertain. Of the 9 who died 4 only took 3 or 4 tablets.

Of the survivors, 17 vomited at once, and all those who took 2 or more tablets vomited within 20 minutes. Of the fatal cases, 3 with doses of 3, 5 and 7 tablets, respectively, vomited within 20 minutes; the time of vomiting in 4 cases could not be ascertained. Sixteen survivors received gastric lavage within 30 minutes, and of

these all who took more than 2 tablets were either lavaged or treated very soon after taking the poison. Of the fatal cases only 2, with 3 and 5 tablets, respectively, received early treatment or lavage.

Twelve, 2 of whom took more than 2 tablets, recovered without parenteral administration of fluids; 13 survivors, of whom 3 took more than 2 tablets, were given parenteral fluids. Of the 9 who died, 1, with 5 tablets, received a hypodermoclysis after 1 hour; 2 were given hypodermoclyses or infusions after 4 or more hours, the others only after intervals varying from 7 hours to 8 days.

The conclusions that can be drawn are that the mortality in bichlorid poisoning depends chiefly upon the amount of the drug taken and absorbed.

The relation of mortality to the symptoms which the patients developed differs, perhaps, in some respects, from other reported series. Among the survivors, with the exception of 2, there is almost complete absence of important symptoms. None had even transitory anuria and only 2 developed significant morphologic urinary changes; 2 had transitory diarrhea, 1 with bloody stools; 4 vomited for 24 hours, but not enough to impair their urinary output, and of these 1 was highly alcoholic, another had chronic gastritis and a third had renal colic; 1 developed a definite mercurial stomatitis. On the other hand, of the fatal cases, all developed diarrhea, vomiting and anuria early, and all but 1 had stomatitis. Two survivors, Cases 44720 and A-6100, who have been omitted from the statistical treatment will be discussed in detail later.

Because of the complete absence of symptoms among survivors it might appear either that the therapeutic measures employed in these cases were peculiarly efficacious in aborting symptoms, but of no ultimate life-saving value; or that the treatments given were of no value and those that survived had not received toxic doses of the poison. It is, however, possible to adopt an entirely different point of view, concluding that mortality statistics are of little value as criteria of therapeutic methods. There are such obvious distinctions between the fatal and nonfatal cases that statistical treatment is inapplicable, because it involves comparison of incomparables. This is, however, the method which has been generally employed for the evaluation of procedures for the treatment of mercury poisoning. It should be possible to find more valid criteria in a study of the responses of functional disturbances and symptoms to therapeutic measures.

Any such analysis must depend upon a clear understanding of the action of mercury and the manner in which it produces its fatal effect. The distribution of the pathologic lesions which result from mercury is remarkably constant, regardless of the route by which the drug is administered; the intensity of the effect in various organs depends upon the mode of administration. In all cases one finds necrosis of the epithelium of the alimentary canal and the tubular

epithelium of the kidneys, with minor changes in other organs, especially the liver, presumably points at which the mercury accumulates in high concentration during the processes of absorption or excretion. The alimentary tract, and particularly the stomach, suffers more intensely when the poison is taken perorally.¹⁶ There is little doubt that mercury is excreted into the stomach,¹⁹ and by the intestine, liver and kidneys.^{14,25} However, after ingestion of the drug, alimentary tract lesions are probably due to damage produced by the drug before it is absorbed or even by that which is never absorbed, and occur chiefly during the initial hours when the gastric and intestinal walls are exposed to maximum concentrations of the metal.

Sublethal doses of mercury cause profuse diuresis,^{14,25,27} probably by producing a large glomerular filtrate. Even lethal doses, which result in anuria, do not appear to disturb glomerular function greatly, and may even accelerate filtration.²⁵ Such doses do, however, cause necrosis of the renal tubular epithelium, perhaps, as has been suggested, because the poison is concentrated by the process of reabsorption in the tubules.^{13,24} In diuresis produced by mercurials, it has been shown by Keith and Whelan,¹⁴ the majority of the mercury is excreted promptly in the urine. Even therapeutic doses will cause serious poisoning, accompanied by necrosis of the gastrointestinal tract, if diuresis does not occur.²²

The necrotic processes in the kidney are entirely, and those in the alimentary canal are chiefly, confined to epithelial layers and are, in consequence, repairable like other purely desquamative lesions without cicatricial residue.

Death of patients or experimental animals with mercury poisoning is referable, in a large proportion of instances, to none of the pathologic lesions mentioned above, but to a condition resembling surgical shock.^{1,9,15,21} In fact, this condition appears to be responsible for almost all, if not all, of the deaths which occur within the first few days after poisoning. This is true of experimental animals as well as accidentally poisoned humans.

Treatment has, in general, been directed almost entirely to promoting elimination of the poison from or through the gastrointestinal tract by the administration of fluids perorally and by rectum, and by gastric lavage and colon irrigations,^{1,9,16,26,28} procedures which are only secondarily intended to furnish fluids to the body and to allay the irritation and inflammation of the gastrointestinal tract by removing its cause, mercury. Instead of combating shock or providing with certainty for the restoration of the materials lost from the body by reason of vomiting and diarrhea, these cleansing measures are well constituted to exaggerate these losses. Some slight exception to this statement may be taken in behalf of those^{9,10,12,26,29} who have advocated and employed the intravenous injection of saline solutions.

Sansum,²⁷ in 1918, with the idea that the provision of a large volume of fluid immediately after poisoning by mercury might mitigate the effects of the poison by accelerating its excretion, gave intravenous injections of various solutions to dogs shortly after they had received intravenously 4 mg. of bichlorid per kilo, enough to cause death without producing anuria. The injections caused profuse diuresis without any effect on mortality. Haskell,¹⁰ in 1923, found that if dogs were given large amounts of saline intravenously after the administration by stomach tube of lethal doses of bichlorid, 20 mg. per kilo, a large proportion survived. There are certain distinctions between these apparently contradictory experiments that may be significant. Presumably the intravenous bichlorid given by Sansum was conveyed to the kidney in high concentration immediately and had caused irreparable damage before the intravenous fluid could act. The peroral mercury given by Haskell was probably absorbed gradually, so that no large amount was present in the blood at any given time. Under these circumstances the intravenous injections, by promoting diuresis, were able to sweep out mercury through the kidneys in sufficient dilution to prevent or mitigate the usual tubular necrosis. Haskell furthermore not only attempted to prevent early vomiting, but also continued his injections, intravenously or intraperitoneally, at intervals of 24 hours or less, thus insuring an adequate supply of fluids to replace those lost by vomiting and diarrhea.

In patients who, having survived a period of several days of anuria, die subsequently^{1,5,16} the urine volume usually remains scanty, azotemia persists and edema is not infrequent. The few blood chemical examinations which can be found in the literature show that in this state the constitution of the blood is profoundly altered.⁵ Postmortem examination may reveal extensive reparative processes, especially in the kidneys, where the tubular epithelium may be largely regenerated.

Although the necessity of furthering elimination of the poison is not to be neglected, it has become increasingly evident in the course of this study that major emphasis must be placed on the restoration and maintenance of an optimum internal environment and the prevention or rectification of the functional disturbances caused by mercury. Consideration and study of these factors has led to repeated modification of therapeutic measures, with the final adoption of a rather radical procedure which, in its entirety, has been employed in the treatment of only 3 cases. The chief aims of the treatment, after the usual preliminary measures have been employed to remove poison from the stomach, are: to prevent shock, to prevent fluid depletion by reduction of vomiting and diarrhea, to replace fluids lost on account of these symptoms, to furnish sufficient fluids to favor the production of a large urine volume, to prevent starvation acidosis and to mitigate protein destruction and to pro-

duce and maintain an internal environment as nearly normal as possible. It is believed that such an environment must exert a favorable influence, if for no other reason, because it will better enable the subject, if he survives the first acute impacts of the poison, to reap later the full advantages of the reparative processes.

The first point which demands consideration is shock, which may come on early and has usually been ascribed to trauma of the gastrointestinal tract. Although this may play its part in precipitating shock, fluid loss by vomiting and early diarrhea may be quite as important. Among the survivors in Table 1 it will be seen that Case 61806, within a short time after taking mercury, and without any treatment other than emesis and lavage, had serum proteins of 8.46 per cent and chlorids of only 92 milliequivalents, indications of hemoconcentration and chlorid depletion. In Case 51558, although the serum proteins are not initially abnormally high, 7.12 per cent, they are distinctly higher than they are 36 hours later, when the patient has received fluids and is voiding freely. Among the fatal cases, 63408 and 41938 illustrate more extreme pictures of the same kind. In the former a blood cell volume of 60.2 per cent renders it the more likely that the high protein value is due to inspissation of the blood. In these cases distinct alkali deficits are evidenced in bicarbonates of 19.2 and 21.7 milliequivalents, respectively. Chlorid is normal in Case 63408, somewhat reduced in Case 41928. The differences in the relative degree of depletion of Cl and HCO_3 depend on the proportions of fluid lost by stomach and by bowel. Vomiting, if the gastric acid secretion is active, will tend to carry out more Cl than base; diarrhea will cause more rapid wastage of sodium. Case 63408, with normal serum chlorids and the lowest bicarbonate, had profuse diarrhea by the time of the blood examination; the others, with chlorid deficits, but less acidosis, had vomited, but had not developed diarrhea.

Whether the blood inspissation be due to loss of fluid in gastrointestinal secretions or to transudation from the vessels such as occurs in shock, it is clear that a situation is early produced which must have an extremely unfavorable influence on the formation of urine. In fact, it is not improbable that initial anuria or oliguria may be due quite as much to reduction of body fluids and low blood pressure as to the destructive effect of mercury on the kidneys. Whatever measures may be employed for the removal of the poison from the alimentary tract, it would seem most rational at this stage to give a large volume of saline parenterally, a procedure which has, indeed, been frequently advocated.^{9,26,29} Early attempts at treatment in this series were directed chiefly toward the support of the fluid and salt stores of the subject and the provision of a large volume of fluid for the production of urine. All patients who continued to vomit after the initial lavage and were unable to take

fluids freely, as well as those who developed diarrhea early, were given large volumes of saline and glucose solutions subcutaneously or intravenously at the earliest possible moment. Ultimately the parenteral administration of fluids as soon as lavage had been completed was made a routine procedure. Those who did not vomit or exhibit diarrhea and who were able to take fluids freely by mouth from the first were given extremely large volumes of water, salty broth and carbohydrate drinks perorally. The quantities of fluid given and the urine volumes produced are indicated in Table 2.

Some idea of the amounts of fluid lost by vomiting can be gained from the magnitude of the apparent positive fluid balances during the first and second days, and also from measurements of vomitus. The immediate generous response of the kidneys is exhibited in the large urine volume. It does not seem unreasonable to suppose that this method of treatment served to minimize the occurrence of shock, to place the organism in a favorable position to resist the general systemic effects of poisoning and, by the establishment of diuresis, to facilitate the rapid excretion of the mercury. Possibly this has something to do with the fact that the survivors in this series were so peculiarly free from symptoms and so sharply differentiated in this respect from the fatal cases. Cases 72767, 72763 and the second observation on Case 51558 (Table 1) show that the chemical composition of the serum after such treatment is relatively normal. The importance of this evidence must, however, be discounted because of the uncertainty concerning the severity of the poisoning in all patients who recovered without symptoms.

The electrolyte patterns in the fatal cases are sharply distinguished from those of survivors. They are characterized by progressively falling serum proteins, low bicarbonate, chlorid and base, with phosphate usually elevated. Reduction of bicarbonate, chlorid and base can be referred, like the similar changes in patients who recovered, to loss of salts in vomitus and feces. The hypoproteinemia is not so easily explained. Loss of protein through the kidneys can be at once excluded because all the patients had anuria or extreme oliguria. Protein starvation may be responsible for reductions late in the course, for example, in the last days of Cases 61163 or 73165; but hardly explain the low value found in Case A-2855, only 12 hours after poisoning. That loss of protein into the intestinal contents cannot be the sole cause of the serum protein deficits is clearly demonstrated by the data on Cases 61385, 44720 and A-6100. In the last 2 patients, especially, serum proteins fell in the absence of diarrhea.

Erlanger⁶ first pointed out that in the later and more severe stages of shock the vessel walls become permeable to proteins, which, therefore, escape from the blood serum into the transudates. In this stage the serum proteins and blood volume diminish simultaneously. Blalock³ finds that transudation of proteins may occur in

a variety of conditions analogous to shock, especially when the blood pressure is low or falling and that, in these circumstances, intravenous injections of salt or sugar solutions may tend to accelerate the escape of serum proteins. The rapidity with which hypoproteinemia developed in these cases, and especially in Cases A-2885 and 73165, is highly indicative of such a seepage of proteins from the vessels. It is obvious that once such a process is instituted a peculiarly vicious cycle has been established, because the force opposed to transudation, the effective colloid osmotic pressure, the difference between the concentration of protein in the blood serum and that in the interstitial fluids, is doubly reduced by reason of the fact that the interstitial fluids receive the protein lost by the serum.

The importance of shock as a feature of early severe mercury poisoning can be illustrated best by certain examples:

Case Reports. CASE 1.—(A-2885.) A woman, aged 55 years, took 5 bichlorid tablets with suicidal intent. About $1\frac{1}{2}$ hours later she was found in the cellar, vomiting and having watery bowel movements. She was brought immediately to the hospital in a condition of shock, with cold hands and feet, cyanosis, distant heart sounds, an almost imperceptible, rapid pulse and a systolic blood pressure which could not be determined with certainty, but seemed to be about 80 mm. She was still vomiting pink, mucoid material and passing reddish, watery stools. Seven hours later, in spite of the subcutaneous administration of 2500 cc. of saline, she had passed no urine, was still in extreme shock with undetermined blood pressure and the subcutaneous fluid had not been completely absorbed. Continuous intravenous saline infusion was instituted. This brought the blood pressure up to 70/58; but as soon as the infusion was interrupted the pressure fell precipitately. For this reason 17 hours after admission she was given a transfusion of 250 cc. of blood. The blood pressure rose to 88/58, shortly after which she voided about 25 cc. of urine. The improvement in the circulatory condition was maintained for about 48 hours. Vomiting ceased and she was able to take fluids by mouth, but diarrhea and anuria persisted. Two and a half days after admission she again went into shock with falling blood pressure and died. The serum electrolyte study in Table 1 was made shortly before the continuous intravenous infusion was begun.

By the time this patient had come to the hospital she already had shock of sufficient severity to preclude the passage of urine. The administration of saline in this condition was of little value as is evidenced by the fact that it was not even absorbed. That the intravenous infusion was doomed to failure when the serum proteins and blood pressure were both so low is obvious. Blood transfusion given far earlier might have reestablished circulatory efficacy and blood volume at a time when restoration of these functions would have been of more benefit. The early stories of Cases 41938 and 61163 are similar. Case 63408, in spite of an early transfusion of 250 cc., could not be brought out of an extreme state of shock, which proved fatal after about 18 hours.

From these examples and what is known of the physiology of shock one can conclude that, although intravenous administration

TABLE 1.—SERUM ELECTROLYTES IN A GROUP OF CASES OF MERCURY POISONING.

Hosp. No.	Time since poisoning.	Blood.			Serum.						
		Nonprotein nitrogen, mg. per cent.	Oxygen capacity, vol per cent.	Cell volume, per cent.	Protein, per cent.	Albumin, per cent.	Globulin, per cent.	HCO ₃ , m.eq.	Cl, m.eq.	Inorganic P, m.eq.	Total base, m.eq.
72767	57 hrs.	22	16.9	38.5	6.68	5.09	Survivors.	28.8	101.2	...	152.5
72673	12 hrs.	22	...	42.6	7.05	4.87	2.18	23.1	104.2
62494	Few min.	20	20.3	109.2	3.9	157.0
61806	Few min.	33	8.46	6.02	2.44	25.3	91.8	1.7	156.8
51558	90 min.	7.12	24.4	98.0	2.6	150.0
	36 hrs.	28	6.21	3.98	2.23	29.5	97.2	1.9	148.0
							Fatal cases.				
20576	9 days	303	12.3	26.0	6.56	10.4	57.0	16.9	...
A-2885	9 hrs.	67	4.38	1.09	3.29	12.4	114.2	2.5	143.6
63408	4 hrs.	46	...	60.2	7.72	4.88	2.84	19.2	101.8	2.4	155.1
41938	3 hrs.	43	20.6	42.4	9.44	21.7	96.3	...	150.0
	4.5 days	165	12.9	32.3	4.98	11.7	101.3	...	143.0
61163	36 hrs.	66	6.33	4.54	1.79	...	90.0
											No treatment.
											Vomiting and diarrhea; subcutaneous glucose and saline.
											Vomiting and lavage; diarrhea and anuria; in shock.
											Vomiting and lavage; in shock.
											Diarrhea and anuria; received little fluids.
											Vomiting, diarrhea, anuria; some parenteral fluids.
	7.5 days	158	4.44	3.43	1.06	...	82.4
											Vomiting, diarrhea, oliguria; parenteral fluids.
73165	14 hrs.	63	...	41.8	5.20	3.57	1.63	18.2	90.7	1.9	124.0
											Vomiting, diarrhea, oliguria; parenteral fluids.
	4.5 days	90	5.30	3.82	1.48	9.3	88.8	3.9	121.0
											Vomiting, diarrhea, anuria and edema; parenteral fluids.
	7.5 days	144	...	28.4	4.50	3.11	1.39	10.1	93.0	5.2	130.0
											Vomiting, diarrhea, oliguria and edema; parenteral fluids.
	9.5 days	175	4.72	23.7	98.8
											Vomiting, diarrhea, oliguria and edema; parenteral fluids.
	11.5 days	212	...	26.5	5.04	3.50	1.54	10.3	98.0	7.3	142.0

The 3 last cases of the series of survivors are given in Table 3.

of saline may be of value in the early treatment of mercury poisoning without shock, it must be employed as a temporary expedient and with care if the blood pressure shows a tendency to fall. If signs of shock appear immediate blood transfusion would seem to be the logical procedure. Subcutaneous injections of fluid are safer than intravenous; but, because the fluid is more slowly absorbed, may not have so rapid a diuretic effect. In some instances the authors have felt that they were able to avoid some of the ill effects

TABLE 2.—FLUID INTAKE AND OUTPUT OF RECOVERED CASES IN EARLY STAGES.
(Records for the first day seldom include more than a fraction of the 24 hours, because this period covers from admission to 7 A.M. of the next day.)

Hosp. No.	Parenteral fluids on 1st day. ⁵	Vomiting persisting more than a few hours.	Fluid intake, cc.			Fluid output, cc.		
			1st day.	2d day.	3d day.	1st day.	2d day.	3d day.
68155	0	0	6,000	8,700	7,500	3310	8,100	5900
84957	S 2000	0	4,400	10,300	5,200	700	3,400	3300
82858	S 3000	0	6,950	7,480	7,950	3550	5,850	4600
22593	S 2500	0	8,800	12,530	6,690	2050	9,010	7650
	I 3500							
53740	0	0	700 ¹	6,500 ¹	4,600	3200	2,340	2100
72767	S 3000	...	3,400	12,450	6,000	500	5,330	5380
72673	I 400	0	16,900	8810		
81314	S 3000	Once or twice	5,250	5,400	5,100	3550	3,000	3900
36688	0	+ ²	1,800	3,300 ³	2,600	...	1,920	1140
56592	0	0	1,400	4,460	3,100	1000	425	1000
4511	S 5000	0	8,500	8,900	5,100	7800	8,900	5800
10295	0	0	5,000	5,000	4,800	3200	3,000	2600
62494	S 1500	+ ⁴	12,800	12,900	12,100	7500	9,100	8800
61806	S 3000	0	5,400	10,280	6,100	1590 ⁵	4,060	3310
51558	0	+	...	7,860	8,800	...	2,980 ⁶	5470
70851	S 3000	+	6,000	13,800	14,800	2500	11,110 ⁷	8900

¹ Intake and output on 1st day includes 12 hours; on 2d day 3000 cc. fluid subcutaneously.

² Vomiting on first 2 days due to renal colic.

³ Fluid subcutaneously on 2d day.

⁴ On 1st day vomited at least 1000 cc.

⁵ Vomited 1400 cc.

⁶ Fluid subcutaneously on 2d day; vomited 1050 cc.

⁷ On 2d day vomited 1500 cc.; received 3000 cc. subcutaneously.

S, subcutaneously; I, intravenously.

and reap some of the benefits of large infusions, by giving small or moderate amounts of hypertonic (10 to 50 per cent) glucose solution intravenously and simultaneously injecting saline subcutaneously. The well-recognized anemia which regularly develops in all cases of severe mercury poisoning affords another indication for transfusion.

Those patients who survive the first impacts of poisoning can, apparently, be divided into 2 groups: those that have continuous

anuria, in whom death is usually attributed to uremia; others who never develop complete anuria, or, after a period of anuria of variable length, resume urination, passing small volumes of urine, but never attaining adequate excretory function. There are in the literature a few extensive studies of blood chemistry in such cases. The outstanding disturbances are persistent or increasing azotemia and reduction of serum chlorids and bicarbonate.^{2,5,12,17} Hayman and Priestley,¹² and Sunderman, Austin and Camack²⁸ found in 1 case that serum base and proteins were also low. Similar disturbances are found in the last 2 fatal cases in Table 1.

It seems most plausible to ascribe the salt depletion to the effects of diarrhea and vomiting, the hypoproteinemia to the factors which have been discussed above and, in addition, to malnutrition which results from these same symptoms. How serious the salt losses may become is illustrated by Case 73165 (Table 1).

CASE 2.—The patient, a woman, aged 47 years, on March 20, 1929, at 6.30 P.M., swallowed 5 7.5-grain tablets of bichlorid of mercury. She did not vomit until 6.50, when an attempt was made to insert a stomach tube. She was brought at once to hospital, where she was given water, eggs and milk, followed by a gastric lavage. At this time her blood pressure was 160/110. By 7.30 the pressure had fallen to 138/90 and she presented symptoms and signs of shock: extreme weakness and cold clammy skin. She was still vomiting material which contained blood. She was given 3000 cc. of saline subcutaneously and 500 cc. of saline and 500 cc. of 5 per cent glucose intravenously. During the night she took fluids poorly, vomited frequently, had watery diarrhea and passed only small amounts of urine at infrequent intervals. In spite of the enormous quantity of salt which she had received, by the next morning (Table 1), 14 hours after taking the poison, the serum proteins, chlorids, bicarbonate and base were found greatly reduced. The cell volume, 41.8 per cent, and a red blood cell count of 5,000,000 clearly proved that these disturbances were not due to hemodilution. After this she was given intravenous saline infusions of about 1000 cc. daily through the 29th (on the 22d 3000 cc. were given by infusion); besides this, subcutaneously, on the 21st 6000 cc., on the 22d 3000 cc. and on the 23d 5300 cc. and on the 26th 3000 cc. of saline and 5 per cent glucose solution. Altogether she received about 30 gm. of sodium chlorid parenterally daily for the first 5 days. Nevertheless, the salt in the blood continued to diminish. Meanwhile she vomited continuously, sometimes as often as 20 times a day, and, in spite of 2 colon irrigations a day, had from 6 to 22 stools. The urine volume, which had been 1160 cc. on the 21st, dwindled steadily. Exact measurement was, for a time, impossible, because so much was voided with stools. However, complete collections were made on 6 separate days after the 24th and the urine volume was found to vary between 40 and 375 cc., with an average of 165 cc. After about 4 days she developed edema. For this reason subcutaneous injections of fluid were, for the most part, discontinued; parenteral fluid administration was limited to a daily infusion of about 1 liter of saline (an exception was made on the 26th when she received 3000 cc. of saline and glucose by hypodermoclysis). The diarrhea and vomiting nevertheless continued and the urine volume remained small. The edema diminished, but did not entirely disappear. The serum proteins had fallen further and the serum salt deficit persisted. On April 31, 10 days from the onset, she was given a transfusion of 450 cc. of blood.

At this time she was in a desperate condition and quite waterlogged. Attempts to administer fluids and food by mouth were discontinued. Although the vomiting diminished promptly, the diarrhea persisted, the urine volume remained small and she died on April 2, 13 days after admission.

In this case and in Case 61163 (Table 1), which was quite similar, it is evident from the frequency and volume of vomitus that the nutritive value of the food and fluids taken must have been negligible. Indeed it was not inconceivable that, acting as stimulants in the stomach, these materials only caused the secretion of extra salt and fluid which was vomited. In the stomach, and probably in the small intestine, there is a tendency for fluids to be brought into osmolar equilibrium with the blood before or during the process of absorption. Unless, therefore, the fluids and food given were isotonic with the blood, salt, at least, would pass into them and, if they were not retained, would be lost in the vomitus. If giving food and fluids has no nutritive value because of emesis, it becomes tantamount to lavage. As a means of removing poison this might be advantageous were it certain that excreted mercury, after the initial stage, attains a sufficient concentration to produce any serious damage or that it is further concentrated in the process of reabsorption. Whether it does or not, there is grave doubt whether this hypothetical damage is to be weighed heavily against the disorganization of the body fluid composition which results from efforts to dilute or remove the poison by emetic measures or lavage. The theory that fluid administration or lavage allays gastric irritation has even less physiologic support. It has been repeatedly demonstrated that animals with pyloric obstruction can be kept alive for long periods if the fluid lost in the initial vomitus is replaced by saline and no fluids are given by mouth. After the initial irritative vomiting under these conditions gastrointestinal secretion practically ceases. Whether the same would be true of a stomach with a necrotic mucous membrane could not be predicted, but it seemed justifiable to make the test in view of the unfortunate outcome of most patients who had been subjected to the conventional forms of treatment. What has been said of gastric lavage and the promotion of emesis may be equally true of colonic irrigations and encouragement of diarrhea.

In a case reported by Hayman and Priestley,¹² under the Lambert and Patterson treatment, at the end of 6 days of anuria urine flow was resumed, but was inadequate. The blood nonprotein nitrogen continued to mount, finally reaching 247 mg. per 100 cc., while chlorid, bicarbonate, base and protein of the serum were greatly reduced. Meanwhile there had been diarrhea. At this point the Lambert and Patterson treatment was discontinued and daily saline infusions were given instead. Immediately the urine volume and nitrogen excretion increased, the blood nonprotein nitrogen fell and the patient made a rapid and uneventful recovery. The improvement

which Hayman and Priestley attribute to the saline infusions may have been quite as much due to interruption of the colonic irrigations. Choisy and Perrot⁵ have reported a case that died at the end of 49 days. After an initial 3-day period of anuria urination was resumed, but the volume remained small, the blood nonprotein nitrogen continued to rise and, after a period of apparent clinical improvement, she developed mental symptoms, extreme asthenia, anorexia, finally edema. From the onset the serum chlorids were low and remained so until death, except for transient responses to subcutaneous and intravenous saline. Little salt was given parenterally, although she received small daily infusions of hypertonic glucose. From what is known of the rapidity of regenerative processes in mercury poisoning it seems difficult to attribute death in this case directly to the effects of this metal. Landau, Glass and Beiles,¹⁷ who have recognized the salt deficiency which results from the gastrointestinal effects of mercury, claim that the administration of bismuth in large doses (as much as 9 gm. daily) greatly reduces mortality.

In spite of all theoretical considerations, withholding all fluids and omission of lavage and colon irrigations marked a radical break with authority and convention that took no small courage. Happily an opportunity to test the theory in an analogous situation without so serious a breach of convention presented itself at this point:

CASE 3.—A patient* was admitted to the hospital in shock with extreme intravascular hemolysis, oliguria and hemoglobinuria. She had attempted to induce abortion by intrauterine injection of lysol after some pills given by a friend had not proved immediately efficacious. Like the mercury cases cited above she passed, for some days, only small amounts of urine containing little nitrogen, and the nonprotein nitrogen of the blood rose steadily. Throughout this time she suffered continuously from epigastric distress and vomited all food and fluids. The vomitus was bloody. In spite of infusions and hypodermoclyses of glucose and saline the serum chlorids fell to 93 milliequivalents. Furthermore she became distinctly edematous. Finally, after 7 days, the administration of food and fluids by mouth was entirely stopped, and she was given daily infusions consisting of 1000 cc. of 10 per cent glucose and an equal amount of saline. Vomiting ceased almost immediately, the urine volume increased rapidly, her condition improved and the blood nonprotein nitrogen diminished. For 4 days, as long as the epigastric pain persisted, the treatment was continued. At the end of that period she was able to eat and drink without vomiting and the infusions were discontinued.

These experiences led to the adoption of an entirely new course of procedure in the treatment of mercury poisoning, which has now been employed on 3 cases. The general principles involved are: (1) Initial administration of protein and gastric lavage, as before; (2) a large intravenous infusion of saline at the earliest possible moment; (3) blood transfusion if evidences of shock appear; (4) if this cannot be effected at once, simultaneous intravenous injection

* This case will be reported more fully in connection with a study of blackwater fever. The intravascular hemolysis may have been caused by quinin.

of 10 per cent glucose and subcutaneous injection of saline may be used as a temporary expedient; (5) subsequent saline and glucose injections and transfusions in quantities and at intervals so regulated as to insure the presence in the body of a large, but not excessive, supply of fluid of nearly normal composition and to maintain circulatory efficiency; (6) from the onset no fluids are given by mouth as long as there is nausea or vomiting. If there is no diarrhea, rectal treatments are omitted. A single small cleansing enema may be given daily if there is diarrhea, if such treatment seems to relieve the diarrhea, as it sometimes does.

CASE 4.—(44720.) A man, aged 32 years, while intoxicated, took some bichlorid of mercury tablets (he claimed that he had taken 3, but it is doubtful whether he actually took more than 2 and he may have taken only 1), at about 8.50 P.M., March 24, 1932. He arrived in the Accident Ward of the New Haven Hospital at 9.19 P.M., having vomited twice on the way. His blood pressure on admission was 135/100 and general physical examination revealed no important abnormalities. After the usual treatment with protein and gastric lavage he was given, by intravenous infusion, 1500 cc. of saline. At 10.20 P.M. his blood pressure was 120/80. At 10.50 P.M. he was given another infusion of 1500 cc. of saline and simultaneously 1500 cc. of saline and 1500 cc. of 5 per cent glucose subcutaneously. Shortly after the infusion his blood pressure was found to have dropped to 96/64. He was therefore given, at 1 A.M., on March 25, a transfusion of 275 cc. of blood which brought his blood pressure up to 110/90. After the transfusion he had a chill, vomited and at 2.45 A.M. passed dark, bloody urine in which no red blood cells were found.* Between admission and 11 P.M. he had 3 involuntary watery stools and vomited at intervals. For this reason he was allowed to have nothing but cracked ice by mouth. At 4 A.M. the vomitus contained changed blood. Until 5.30 A.M. he passed large amounts of urine without difficulty, but after this did not void again until 1 P.M., after he had been given intravenously 1000 cc. of 10 per cent glucose solution. A similar injection was given at 3 P.M., when there was again evidence that diuresis had been interrupted. After this the urinary volume did not again diminish. After the first 3 bowel movements diarrhea ceased. There was occasional vomiting throughout the 25th, but none after the early morning of the 26th. It was, therefore, possible, after 9 A.M. on the 26th, to discontinue parenteral administration of fluids and to give both food and fluids by mouth. He complained throughout the 25th and 26th of soreness of the mouth, burning in his throat and pains in the loins. These complaints continued through the 27th and by the 28th he had a well-marked stomatitis. Diarrhea recommenced on the 29th and in the course of the day he had 7 loose stools.

On the 30th he vomited large amounts of fresh blood twice and the stools became tarry. Finally at 11 P.M. he had a third gastric hemorrhage succeeded by symptoms of shock. At 1.30 A.M., March 31, his blood pressure was only 90/60. He was, therefore, given, at 2.30 A.M., an infusion of 500 cc. of 10 per cent glucose, followed by a transfusion of 300 cc. of blood. This relieved shock symptoms and restored the blood pressure. All fluids by mouth were, of course, discontinued for 24 hours and large volumes of glucose and saline were given subcutaneously. For the next 2 days hypodermoclyses were continued, but the patient was allowed water by mouth. For 2 days the tarry diarrhea persisted.

After April 1 all symptoms ceased, the stomatitis rapidly cleared and

* In spite of the obvious hemolytic reaction, repetition of agglutination tests seemed to indicate no incompatibility between the blood of donor and recipient.

recovery was uneventful. On April 2 a small transfusion was given to accelerate recovery and Sippy diet was instituted.

The urine immediately after the first transfusion was quite typical of extreme hemoglobinuria and the next few specimens contained changed blood pigment and detritus. Very faint traces of albumin, leukocytes and occasional casts persisted in the urine through April 9.

When discharged, April 12, the only symptoms were fatiguability, probably referable to anemia, and nocturia. April 25, when he was seen in the dispensary, he seemed entirely well except for a moderate anemia.

The record of treatment with some notes on excretory function are presented in Table 3, the results of blood chemical examinations in Table 4.

TABLE 3.—RESULTS OF CHEMICAL EXAMINATION OF THE BLOOD.

Date.	Time.	Blood.			Serum.						
		Oxygen capacity, per cent.	Cell volume, per cent.	Nonprotein nitrogen, mg. per 100 cc.	Protein, per cent.	Albumin, per cent.	Globulin, per cent.	Bicarbonate, m.eq.	Chloride, m.eq.	Inorganic phosphorus, mg. per 100 cc.	Total base, m.eq.
CASE 44720.											
Mar. 24	10.50 P.M.	42	8.16	5.27	2.89	23.6	99.4	3.5	144.1
25	8.00 A.M.	43	8.53	5.78	2.75	25.2	96.5	3.4	147.7
	12.15 P.M.	22.2	52.6	49	8.22	5.95	2.27	23.0	98.3	2.8	143.9
	5.00	20.3	47.9	42	7.18	4.96	2.22	23.2	97.0	3.5	140.5
26	9.00 A.M.	18.7	41.8	59	6.42	4.32	2.10	24.2	98.8	3.4	140.7
27	9.00	69							
28	9.00	16.0	37.9	75	5.61	3.90	1.71	25.2	99.1	4.9	144.7
29	9.00	16.2	37.7	95	5.62	4.01	1.61	25.9	98.6	5.6	142.7
30	9.00	13.1	28.4	85	4.96	3.61	1.35	23.1	101.4	6.2	147.8
31	2.00 P.M.	81							
April 1	2.00	8.1	19.6	63	5.17	3.30	1.87	22.9	104.2	4.0	145.1
2	2.00	6.7	15.8	46	4.53	3.08	1.45	23.3	105.5	3.5	147.5
25	9.00 A.M.	13.8	34.6	28	7.09	4.57	2.52	27.1	102.6	3.4	
CASE A-6100.											
Mar. 29	9.15 P.M.	..	54.3	69	7.44	5.45	1.96	16.8	97.8	4.8	141.1
30	7.15 A.M.	21.3	49.0	63	6.04	4.61	1.43	17.3	104.0	5.5	139.2
31	7.15	17.3	39.5	85	5.22	3.66	1.54	17.3	98.2	4.1	137.3
April 1	9.00	17.0	39.8	97	5.39	3.66	1.80	15.0	91.6	4.5	132.9
3	2.00 P.M.	140	5.47	3.80	1.70	13.7	95.8	6.9	138.8
5	9.00 A.M.	16.7	38.3	130	5.66	3.95	1.70	15.1	95.5	7.4	139.3
6	9.00	141	5.95	3.84	2.12	16.4	93.9	6.7	136.5
8	9.00	16.3	35.1	128	6.63	3.69	2.97	17.1	102.0	8.5	142.0
11	9.00	17.4	41.3	117	7.37	4.02	3.34	16.1	100.0	7.9	145.0
14	9.00	..	31.8	120	5.98	3.26	2.70	14.9	97.5	7.1	136.5
19	9.00	12.7	29.0	84	5.64	3.29	2.35	17.7	102.0	6.1	137.3
25	9.00	35	4.77	3.24	1.53	23.5	99.9	3.2	141.3
CASE 61385.											
May 10	9.00 A.M.	30	6.96	5.09	1.84	25.9	100.9	3.0	
11	9.00	19.0	48.3	30	6.76	4.88	1.88	25.0	99.0	4.3	
12	9.00	16.1	40.5	23	5.45	4.05	1.40	26.2	103.1	3.0	

TABLE 4.—CLINICAL DATA OF CASE 4 (44720).

"Time," in relation to parenteral fluids, until after 8 A.M., March 26, indicates approximately the time at which injections were begun; "time," in relation to excreta, represents the time at which these were collected.

Date, 1932.	Time.	Fluid intake.			Fluid output.			Chlorid.			Blood pressure.
		Intravenous, cc.	Subcutaneous, cc.	Oral, cc.	Urine, cc.	Vomitus, cc.	Feces, cc.	Intake, gm.	Urine, gm.	Vomitus, gm.	Feces, gm.
Mar. 24 . . .	9.00 P.M.	1500	3 lost ⁴	13.5	5.0	...	135/100
	10.00	1500	650	13.5	6.0	...	120/80
	11.00	...	3000	...	640	13.5	7.8	...	128/118
	12.00	880	0.7	3.9	...	92/84
Mar. 25 . . .	1.00 A.M.	350 ¹	...	200 ²	400	1700	...	13.5	4.5	2.6	...
	3.00	...	2000	250 ²	370	13.5	1.7	...	110/90
	6.00	1000	130	110/85
	11.00	107/82
	1.00 P.M.	1000	290	2.2	...	115/90
	3.00	250 ²	270	1.8	...	130/100
	4.00	130/95
	5.00	...	2000	...	155	13.5	1.0	...	125/90
	6.00	100	560	0.7	...	124/85
	8.00	500 ²	105	0.8	1.2	124/85
	9.00	100	0.6	...	125/85
	11.00	155	0.8	...	125/95
Mar. 26 . . .	3.00 A.M.	260	1.3	...	130/95
	8.00	4350	1035	...	100 gm.	0	1.8	0	130/90
Mar. 26 . . .	9.00	130/85
to 27 . . .	9.00	2494	4.7	...	130/90
to 28 . . .	9.00	4505	3130	...	0	135/95
to 29 . . .	9.00	4000	1800	100	4.9	...	130/100
to 30 . . .	9.00	600	...	3100	1795	2.7	1.8	2.0	142/100
Mar. 31 . . .	2.00 P.M.	400 ³	5000	300	1380	1500	...	36.9	2.2	5.0	125/80
April 1 . . .	2.00	...	3000	2500	1260	721	...	27.0	3.3	1.2	120/65
April 2 . . .	2.00	...	3000	2550	1750	...	57	27.0	6.6	...	120/70

¹ Transfusion of 275 cc. blood with 75 cc. of saline.

² Transfusion, 300 cc. blood with 100 cc. saline.

⁴ Three involuntary watery stools lost.

³ Cracked ice.

It is obvious that as a test of therapeutic measures this case is not entirely satisfactory. In the first place the dose of mercury which he took is not certain and probably not large enough to prove lethal. He does, however, appear to have absorbed enough to produce definite signs of poisoning: diarrhea, vomiting, stomatitis, temporary reduction of urine excretion (on the morning of March 25) and accumulation of blood nonprotein nitrogen and serum inorganic phosphate. Early blood examinations reveal hemoconcentration (high serum proteins and cell volume). Early signs of shock appeared shortly after admission. Unfortunately the response to therapy and the symptoms and functional disturbances immediately succeeding the first transfusion are confused by the occurrence of hemoglobinuria. Later a still more serious complication is introduced by the gastric hemorrhage. It may be argued and it was greatly feared that this might be referable to the effect of withdrawal of fluids in the face of mercurial ulceration. However, by the time of this accident he had been for 3 days taking food and fluids freely without gastric symptoms. Moreover, it was found that the patient had attended the Medical Dispensary during the preceding summer for a condition that was suspected to be gastric ulcer. Roentgen confirmation was not secured because he ceased attending the clinic before Roentgen ray examinations could be made. Barium Roentgen rays taken just before his discharge from the hospital disclosed no signs of gastric ulcer; but, by this time he had been for some days on Sippy treatment, free from symptoms. Except for these adventitious conditions, the course was singularly free from the distressing signs and symptoms usually seen in poisoned patients.

Although the serum proteins, hemoglobin and cell volume fell and the nonprotein nitrogen rose even before the gastric hemorrhage, diarrhea and vomiting early ceased, urine volume was maintained, no edema developed and the electrolytes remained relatively normal. Alkali deficit never became important; serum chlorids were only slightly reduced in the early days, perhaps because the parenteral fluids contained too little sodium chlorid in proportion to glucose and water.

One might conclude that the patient had been enabled by the therapy to escape many of the miseries of poisoning, if not death itself, even in the face of hemoglobinuria and a gastric hemorrhage which was in itself a serious hazard. On the other hand it is almost possible to take the gloomy view that therapy was responsible for these accidents and that only divine grace saved him.

CASE 5.—(A-6100.) A male, aged 60 years, at 6 P.M. on March 28, 1932, with suicidal intent, swallowed 3 mercury tablets dissolved in water. He vomited almost immediately and after this was unable to take any food and vomited all fluids. He also developed, within a very short time, a profuse diarrhea with frequent watery stools. This persisted until he was admitted to the New Haven Hospital at about 9 P.M., March 29.

Up to this time he received no treatment. On admission he appeared thin and extremely dehydrated; his blood pressure was 120/80, but rapidly fell to 106/82. He was given at once, by intravenous infusion, 1000 cc. of 10 per cent glucose solution, and by hypodermoclysis 3000 cc. of saline. The blood pressure at 10 P.M. was only 90/80, but rose again after 30 minutes, remaining for the rest of the night between 100 and 120 mm. From the onset he passed no urine. The diarrhea, which had persisted until his admission to the ward, ceased abruptly at this time and was succeeded by obstipation. Both anuria and obstipation persisted until April 2. On this day, after an enema, 469 gm. of feces were removed, and on the same day he passed 18 cc. of urine. After this the urine volume gradually increased.

From the outset he was able to take fluids by mouth, vomiting only once, on April 2. The first night he received only 900 cc. of carbohydrate fluids orally. The next day, March 30, he drank freely until late in the afternoon, when he was given a hypodermoclysis of 1500 cc. of saline, because he complained that he was too full to drink. March 31, because of the same symptoms, 4000 cc. of the total 5600 for the day were given parenterally. On April 1 he vomited a small quantity and was given 1200 cc. of saline subcutaneously. After the enema on April 2 he again had no bowel movements for 3 days. On the 6th and 8th he was given cleansing enemas because of the persistent obstipation. On the 9th he had a spontaneous bowel movement and after this developed a troublesome diarrhea. This consisted of the frequent passage of small watery spurts, at first containing fresh or changed blood, with considerable tenesmus. The volume of the stools was very small as is evident from the fact that the total weight of material passed in 18 movements on the 11th and 12th amounted to only 659 gm. The diarrhea, which was accompanied by low-grade fever, persisted when he left the hospital against advice on April 29.

The first urine voided on April 2 gave a heavy reduction for albumin and was loaded with cellular debris. Subsequent specimens contained diminishing amounts of albumin, cells and casts. The urine of April 28 had only a faint trace of albumin and an occasional hyalin cast.

In spite of the early anuria and obstipation and except for the later diarrhea, the patient was peculiarly free from symptoms. His only complaint for the first few days was a sense of fullness when he tried to drink large quantities of fluid and regret that he was given no nourishment but carbohydrate fluids. From April 6 on he ate a general mixed diet.

The chief data pertaining to therapy and to excretory function are presented in Table 5, the results of chemical examinations of blood in Table 3.

There can be little doubt that this patient received a toxic and possibly lethal dose of poison, 3 tablets in solution. That much of this was absorbed seems evident from the fact that he developed quite early all the symptoms of severe mercury poisoning: anuria, vomiting and diarrhea. The prognosis was peculiarly unfavorable because he received no treatment for more than 24 hours. The first chemical examination of the blood, immediately after admission, revealed a high degree of hemoconcentration (cell volume, 54.3 volumes per cent) with serious depletion of bicarbonate, chlorid and base and well-marked accumulations of nonprotein nitrogen and inorganic phosphate. Evidences of shock were slight and disappeared rapidly after administration of saline and glucose solutions without the need of a transfusion.

TABLE 5.—CLINICAL DATA OF CASE 5 (A-6100).

Date.	Fluid intake.	Fluid output.			Cl (as NaCl).				Blood pressure.	Sodium bicarbonate, gm.	Weight, kilos.
		Urine, cc.	Vomit, cc.	Stools, number.	Intake, gm.	Urine, cc.	Vomit, cc.	Feces, gm.			
Mar. 29	4900 ¹	0	0	0	27.0	0	0	0	120/80	0	
30	4100 ²	0	0	0	13.5	0	0	0	120/90	0	
31	5600 ³	0	0	0	13.5	0	0	0	130/90	0.7	
April 1	2300 ⁴	0	232	0	11.6	0	0.7	0	130/80	2.0	66.9
2	1620	18	0	469 gm. ⁶	4.0	0.1	0	0.1	140/100	2.7	67.5
3	2920	1032	0	0	16.2	5.4	0	0	150/100	0.6	67.9
4	3270 ⁵	2025	0	0	13.5	12.2	0	0	150/100	2.0	
5	3045	2398	0	0	3.1	13.9	0	0	...	0	
6	2090	3530	0	1 ⁶	9.3	20.0	0	0	...	0.6	
7	3145	3800	0	0	9.3	20.3	0	0	...	0	62.0
8	3050	2560	0	1 ⁶	8.8	12.4	0	0	...	0	60.1
9	3930	1960	0	1	9.1	7.5	0	0	...	0	
10	1900	1500	0	2	6.6	4.5	0	0	...	0	60.3
11	4120	660 gm. ⁷	9.7	0	0	0.9	170/100	2.0	58.7
12	1750	890	..		9.2	1.2	0	0	148/98	2.0	58.7
13	2110	1260			8.0	2.6			...	2.0	58.8
14	2850	1740			8.0	2.6			...	2.0	58.6
15	2280	1720			6.0	6.6			136/90	2.0	58.5
16	3550	2260			8.4	6.9			130/90	2.0	57.6
17	3130	2090			8.9	6.4			128/88	2.0	57.3
18	2050	2110			8.5	6.3			...	2.0	57.3
19	2180	1800			8.1	6.0			...	2.0	57.4
20	1970	1580			8.3	5.9			...	2.0	57.3
21	1900	1700			7.1	5.6			...	2.0	57.0
22	2200	1680			6.6	4.7			...	2.0	57.1
23	1950	1480			7.7	4.4			...	2.0	56.5
24	1600	1210			8.8	4.6			...	2.0	56.2

¹ 1000 cc. saline intravenously; 2000 cc. saline and 1000 cc. 5 per cent glucose subcutaneously.

² 1500 cc. saline subcutaneously.

³ 1500 cc. saline and 2500 cc. 5 per cent glucose subcutaneously.

⁴ 1200 cc. saline subcutaneously.

⁵ 500 cc. 10 per cent glucose and 1500 cc. saline intravenously.

⁶ Result of enema.

⁷ Onset of diarrhea; 13 stools on April 11, 5 on April 12.

It is not improbable that the administration of fluids during the first days was overemphasized. Although the patient developed no demonstrable edema during the anuria period, the rapid loss of weight in the first days following resumption of urination suggests that the body had been previously somewhat overloaded with fluid. That the balance between salt and water in the fluids given was also somewhat irregularly and imperfectly maintained is evidenced by the fluctuations in serum chlorid and base. Between the first 2 electrolyte studies the major portion of the fluid given was saline, which caused serum chlorid to rise to a rather high level. During the succeeding 48 hours larger amounts of water and less saline were given, causing serum chlorids and base to fall to a very low

level. Bicarbonate remained consistently low. The initial reduction of bicarbonate and base was presumably referable to diarrhea. The failure of these 2 components to rise after chlorid administration is natural. With ablation of renal function the ability to excrete the Cl ion of chlorid, retaining the base to reconstitute bicarbonate, was lost. Only by supplying bicarbonate as such could the electrolyte pattern have been restored to normal. Small quantities of sodium bicarbonate were given with this end in view, but this therapy was not pushed for fear of precipitating vomiting, which seemed a greater evil than the alkali deficit.

Withdrawal of oral fluids was not necessary in this case, for more than brief intervals, because vomiting had ceased by the time he entered the hospital. Restriction of oral fluids and substitution of subcutaneous and intravenous fluids were employed at intervals when nausea and vomiting threatened. There was, of course, no intention of producing such complete obstipation. How far treatment may have been responsible for the condition is uncertain. Restriction of the diet to easily absorbable sugars may have played a part. The results indicate that the patient recovered from most of his symptoms without the lavage processes usually employed and without the intervention of the bowel. This supports the theory that mercury causes its chief effects shortly after administration. It would certainly seem more advisable in future cases to employ enemata at daily intervals to assure removal of fecal accumulations and any poison that they might contain. Whether the diarrhea that developed on April 11 can be attributed to mercury is uncertain. June 1 the patient was in excellent health and stated that he had only intermittent brief periods of diarrhea. His wife volunteered that these seemed to occur only when he worked.

The wellbeing of the patient after treatment was instituted and his freedom from the usual distressing symptoms were most striking. One is forced to wonder whether vomiting and diarrhea and perhaps the constant lavage of the gastrointestinal tract are not responsible for some of the distress commonly experienced by subjects seriously poisoned with mercury.

The anuria and hypoproteinemia became progressively more severe, even after the blood nonprotein nitrogen had begun to fall. It is obvious that the initial fall of serum protein cannot be due to gastrointestinal protein loss. Hemodilution may have played a part. Between April 5 and 10 when the urine volume first became large the proteins rose sharply. The subsequent fall can, perhaps, be attributed to malnutrition resulting from inadequate diet and diarrhea together.

CASE 6.—(61385.) A married woman, aged 20 years, at 9 P.M., May 10, 1932, took 1 bichlorid tablet with suicidal attempt. She was almost immediately given egg white and mustard and vomited within 15 minutes. By 9.15 P.M. she was in the Accident Ward of the New Haven Hospital,

where she received gastric lavage, followed by an intravenous infusion of 1000 cc. of 10 per cent glucose solution and subcutaneous injection of 1500 cc. of saline and 500 cc. of 5 per cent glucose solution. Her blood pressure on admission was 137/76 and fell to 120/80 before she was sent to the medical ward. When she was still in the Accident Ward she voided 750 cc. of urine. Attempts to administer fluids by mouth provoked vomiting and were, therefore, discontinued at 2.30 A.M. At 5 A.M. she received by hypodermoclysis 2000 cc. of saline because of vomiting and mild diarrhea. During the night she urinated 4 times, twice with stools, and had 4 bowel movements. At 9 A.M. she appeared drowsy and complained of nausea and epigastric pain. Oral administration of fluids, which had been resumed at 8 A.M. was discontinued after a short time because of renewed vomiting, and she was given, in the course of the day, 1000 cc. of saline and 1000 cc. of 5 per cent glucose subcutaneously and 500 cc. of 10 per cent glucose solution intravenously. By evening nausea and diarrhea had ceased and she was able to take peroral fluids. Improvement continued through the night and by the morning of May 12 she was without symptoms and able to take a regular diet.

From admission until 10 A.M. the next morning the total excreta (urine, stools and vomitus) amounted to 1770 cc. and from 10 A.M. on May 11 to 7 A.M. on May 12, 3160 cc. It was impossible to separate urine and feces accurately. However, it is estimated that the second specimen contained about 600 cc. of fecal matter and 300 cc. of vomitus. The uncontaminated urine specimens which were collected contained no albumin and no significant microscopic abnormalities.

The results of chemical examinations are presented in Table 3.

In this case it seems reasonably certain that the dose of poison taken, though sufficiently large to cause diarrhea and vomiting, would probably have caused no serious damage nor proved a threat to life. The chemical studies show none of the common disturbances of the electrolyte pattern which have been demonstrated in some of the earlier cases of the series who had taken only enough poison to provoke vomiting. The administration of subcutaneous and intravenous fluids and the discontinuation of oral fluids in the presence of nausea and vomiting may have been instrumental in preventing such disturbances. It is interesting to note that, in spite of the absence of symptoms and functional disturbances, the serum proteins, hemoglobin and cell volume fall rapidly, reaching a distinctly subnormal level 36 hours after poisoning. By this time symptoms had disappeared and the urine output was quite adequate, making hemodilution rather unlikely. The consistency with which anemia and hypoproteinemia develop after mercury suggest some injury to the systems which control regeneration of red cells and serum proteins.

Summary. Although the outcome in these cases can in no sense be considered as a vindication of the course of therapy which has been proposed, the results in Case 5 (A-6100) at least justify the hope that it may prove superior to previous procedures. At least it seems reasonable to devote more attention to the functional disturbances that result from mercury poisoning, even if this necessitates a certain degree of moderation in eliminative measures. The

intention is not to propose a routine procedure, quantitatively measured and unalterably fixed for all patients alike; but rather general principles of treatment aimed against the most serious effects of the poison. The application of these principles and the emphasis placed on particular procedures must be adapted to the individual patient. It is obvious that this requires coördination of judgment and effort. The authors have frankly admitted that the ideal combination of these qualities was not attained in the treatment of the 2 serious cases described above. In Case A-6100 a point was stretched when the obstipation was allowed to continue, chiefly because as long as the general condition of the patient seemed so good it appeared justifiable to subject the treatment to an acid test.

It is believed that the general therapeutic principles which have been suggested are applicable to the treatment of other types of poisoning attended by gastrointestinal irritation or injury and renal damage, or in which the elimination of a poison which causes irritation or injury of the gastrointestinal tract may be facilitated by the production of diuresis. Its application in a case of phenol poisoning with hemoglobinuria has already been mentioned. More recently it has been employed successfully to combat the effects of rat poison (chiefly phosphorus) in another subject.

Conclusions. Major emphasis in the treatment of mercury poisoning has in the past been laid upon measures aimed to promote elimination of the poison through the gastrointestinal tract. Such measures have tended to exaggerate rather than to alleviate the functional and chemical derangements within the body which are caused by mercury. Chief among these are shock, reduction of the fluid content of the body and salt depletion.

General principles of treatment have been proposed, involving radical departures from previous procedures, which have as their chief aim prevention or alleviation of shock, dehydration and salt depletion, the provision of adequate body fluids of normal composition and the maintenance of optimal renal function.

The application of these measures in 3 cases is described in detail.

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OSTEOSCLEROTIC ANEMIA.

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THE term osteosclerosis is understood to include those rare affections of the skeleton in which the bone marrow is encroached upon or obliterated by proliferation of connective tissue or deposition of bone, leaving the bones compact and dense but without change in their outward contour. Two types of the disease are recognized, that of so-called marble bones and myelosclerosis. The former, recently reviewed by Karshne and Pirie, seen usually in children and young adults, is hereditary and is characterized by a heavy deposition of bone of low phosphorus content advancing from the diaphyses. In the roentgenogram a homogeneous density, first compared to marble by Albers-Schönberg, obliterates the bony structure. A history of repeated fractures is frequently obtained.

The second type is not familial and multiple fractures have not been described. The pathologic process is largely a diffuse increase of connective tissue or trabeculae in the marrow space, leaving the cortex still recognizable. The appearance of the bones in the roentgenogram is that of moderately increased density but with most of the cortex still evident. This contrast in the two types is shown in the accompanying illustrations.

Progressive osteosclerosis crowds out the marrow cells and often

produces a severe anemia with compensatory hemopoiesis in the spleen, liver or lymph nodes. Such a myelophthisic anemia may occur in either the Albers-Schönberg group or in myelosclerosis.

The purpose of this paper is to present 2 cases of this second type of osteosclerosis in which such an anemia was the outstanding feature. As descriptions of this type, except for Donhauser's report in 1908, have not been found in the American literature these cases are deemed to be of exceptional interest.

Case Reports. CASE 1.—An Italian, aged 42 years, entered the hospital on October 28, 1929, complaining of weakness for 10 months. He had been losing weight and strength and in May, 1929, gave up work to go to Italy, where his doctor placed him on a regimen of cooked liver. He improved somewhat but by the time of his return to Boston, in September, weight loss and dyspnea on exertion led him to enter the hospital. The tongue had not been sore and his diet had been well balanced.

In the *family history* no one had sustained fractures. One sister in Italy had had an anemia that responded to liver. He had 4 children who were healthy and their pelvis, femora and knee joints showed no evidence of disease by roentgenogram.

In the *past* he had been well and strong and had broken no bones. The *occupational history* was interesting in that he had been a glass polisher for 12 years, using a buffing wheel with red oxid of iron as a rouge. A slight amount of dust was in the air about this wheel. No exposure to lead or benzol was suggested.

Physical Examination. He was well developed but undernourished and showed a sallow skin with a hectic flush over the malar eminences. The sclerae were clear and no petechiae were seen. There was no glandular enlargement. The head, eyes, lungs and heart were normal. The blood pressure was 120 systolic and 80 diastolic.

The radials and brachials were not sclerotic and the fundi showed normal vessels. A moderately firm, nontender liver and spleen were felt at the costal margins. There was some tenderness on deep pressure over the medial condyles of the femora and extreme flexion of the knees and extension of the elbows were painful. The clavicles were prominent and seemed thickened. The remainder of the examination was not remarkable.

Laboratory Examinations. *Urine:* normal; no Bence-Jones protein. *Blood:* red blood cells, 2,500,000; hemoglobin, 45 per cent (Tallqvist); white blood cells, 4100 (polymorphonuclears, 54; lymphocytes, 38; mononuclears, 5; myelocytes, 3 per cent); blood smear (Wright) showed marked polychromasia with variation in the size and shape of the red blood cells (3 normoblasts were seen and the platelets were decreased); bleeding time, 6 minutes; clotting time, 2 minutes; fragility of red blood cells normal (B.H., 0.44 per cent; C.H., 0.32 per cent); average red cell diameter, 7.2 micra (dried smear). Hinton and Wassermann tests negative. Serum agglutinations negative in all dilutions for melitensis, porcine and bovine abortus. Blood cultures showed no growth on three trials.

Gastric analysis with ergamin normal. *Liver function* normal. (Rosenthal, 2 per cent retention in one-half hour.) Basal metabolic rate, +9. Roentgenograms of the heart and lungs were normal. A gastrointestinal series showed the duodenal cap slightly enlarged and the first portion of the duodenum small and flattened but no diagnosis was offered after second examination.

The pelvis, vertebrae, ribs and long bones showed diffuse increase in the bone density but the cortex could be distinguished. No fractures or areas of destruction were seen. *The skull* was normal.

Course. In spite of a persistent reticulocyte count of 1 to 3 per cent, the blood level did not change appreciably with liver and iron therapy. An afternoon fever of 99° to 100° F. continued while he was at rest in bed. Frequent sweats either in the day or night troubled him. A biopsy of a gland, 1 cm. in diameter, from the right supraclavicular area was diagnosed as chronic inflammation. In the period of 1 week three tarry, guaiac-positive stools were passed. This incident was never explained and with careful search no further blood loss was discovered.

After a 5 weeks' study a satisfactory diagnosis was not reached, but splenic anemia (Banti) was favored and exploration for splenectomy was advised but the patient decided to deliberate on this at home. The significance of the previous Roentgen examination had been overlooked at this time.

On May 6, 1930, he returned, saying that he has spent much of the time in bed, taking a high vitamin diet and 6 Bland's pills daily. He complained only of weakness and pains in the joints. There had been no obvious blood losses. The heart was now found to be enlarged 10 cm. to the left in the fifth interspace and a low-pitched, systolic murmur was heard, loudest at the second left interspace. The spleen was 4 cm. below the left costal margin and a smooth liver edge was felt 4 cm. below the right mid-costal margin. Slight pitting edema was present over the ankles.

Repeated laboratory examinations showed no significant changes except for a red blood count of 1,300,000 and a hemoglobin of 25 per cent. The blood smears again contained numerous immature forms. Additional blood cultures and serum agglutinations for undulant fever were negative. A therapeutic trial with quinin did not alter the febrile course. Finally, aided by the previous roentgenologic report, the diagnosis of osteosclerotic anemia was made after bone marrow biopsies were done.

Biopsy Report (Dr. T. B. Mallory). *Bone Marrow.* Microscopic examination shows a very slight increase in the number and width of the bony trabeculae. There is no osteoid tissue and no evidence of active bone formation. The spaces between the bony trabeculae are filled with fatty and fibrous tissue with minimal numbers of myeloblastic cells. Scattered stem cells, myelocytes and occasional megakaryocytes are recognized. Plasma cells are present in moderate numbers. A few cells with round pyknotic nuclei and no cytoplasm are seen which may represent normoblasts, but their identification is uncertain.

Sternum. The picture is essentially similar. Evidence of proliferation is scant but there is marked fibrosis of the marrow and aplasia of both myeloid and erythroblastic elements, the latter being most markedly affected.

Although it seemed unlikely that this was a metabolic disease, investigation of the calcium and phosphorus metabolism was done. These results were normal as compared with studies on normal individuals by Bauer, Albright and Aub.

TABLE 1.—CALCIUM AND PHOSPHORUS METABOLISM.

	Period 1 (3 days). Mg.	Period 2 (2 days). Mg.
Calcium intake	279.0	186.0
Phosphorus intake	1911.0	1274.0
Urine, calcium	123.0	107.0
Feces, calcium	436.0	505.0
Urine, phosphorus	1709.0	797.0
Feces, phosphorus	447.0	526.0
Serum, calcium	10.9	9.7
Serum, phosphorus	4.0	4.1

Between May 6 and September 27, 1930, the patient spent all but 4 weeks in August in the hospital. His general condition improved and the blood level was maintained about 2,000,000 by five direct transfusions of 500 cc. at intervals of 3 to 4 weeks.

From October, 1930, to March, 1932, he has been closely followed by Dr. C. W. Heath, in the Thorndike Memorial Laboratory of the Boston City Hospital. Trial periods with a low calcium diet combined with ammonium chlorid and Lilly's liver extract, 343 (the daily equivalent of 300 gm. liver), combined with a high calcium and later a high phosphorus diet produced no remarkable change.

On October 30, 1930, he was given 0.9 cc. of adrenalin intramuscularly. In 15 minutes the red blood cells increased from 2,400,000 to 2,600,000; the white blood cells from 4100 to 19,000 and reticuloocytes from 4 to 8.2 per cent and the myelocytes from 1 to 4 per cent. At the end of 5 hours the entire formula had returned to approximately the first figures.

By November 9, 1931, (when he was readmitted) the anemia had slowly advanced to 900,000 red blood cells, with a hemoglobin of 13 per cent (Sahli). The white cells numbered 15,000, showing numerous myelocytes and myeloblasts. Reticuloocytes ranged from 7 to 9 per cent. While in the hospital he was given Fowler's solution for 13 consecutive days, reaching a dose of 28 minims daily. There was no objective change until 12 days after the last dose, when, with red blood cells 600,000, he developed air hunger. Two citrate transfusions were then given 1 week apart and the patient gained strength rapidly so that he was able to leave the hospital the second week after this incident. Coincident with the rise in red blood cells to 1,400,000, the white blood cell formula returned to the previous level.

Roentgenograms of the skeleton taken at this time showed no change from those taken 14 months earlier.

When last seen, September 15, 1932, the severe anemia was still present, but he was able to be up and about the house.

CASE 2.—A Scandinavian stone cutter, aged 54 years, entered the hospital on March 7, 1931, complaining of weakness and anemia of 10 months' duration. He had been quite well until the preceding June, when he noted pallor and easy fatigability. In November, 1930, weakness and dyspnea on exertion forced him to stop work and on his local physician's advice he took 3 vials of a liver extract daily for several weeks but without relief.

The family history was noncontributory and he had 1 healthy son. In the past he had typhoid fever at 25 years, but gave no history of rheumatic fever, nor did he remember breaking any bones. His occupation for 30 years had been cutting granite paving blocks with a short-handled, pneumatic "plug drill." This work was in the open without protection against the moderate amount of granite dust. There was no exposure to lead or benzol.

Physical Examination. He was a well-developed, pale, gaunt man in no distress. The skin and mucous membranes were pale, with scattered petechiæ over the trunk and in the nail beds and conjunctivæ. The head and chest showed nothing unusual, except for a heart that was enlarged 10 cm. to the left in the fifth interspace and 5 cm. to the right in the fourth. The sounds were of rapid, regular rhythm with low pitched, systolic and diastolic murmurs along the left sternal margin, heard in the recumbent position. Blood pressure was 130 systolic and 58 diastolic. The pulses were equal and synchronous with poorly sustained tension. Examination of the fundi showed multiple, minute hemorrhages in the retina. The liver dullness extended from the right fifth rib to the costal margin and the spleen edge was felt 3 cm. below the left midecostal margin. The prostate, extremities and reflexes were normal.

Laboratory Examinations. *Urine:* normal; no Bence-Jones protein. *Blood:* red blood cells, 1,200,000; hemoglobin, 35 per cent; white blood cells, 3600 (polymorphonuclears, 65; lymphocytes, 11; mononuclears, 3; basophils, 5; myelocytes, 14; myeloblasts, 2 per cent); the smear showed marked polychromasia with variation in the size and shape of the red cells (the number of platelets was reduced); average diameter of red blood cells, 6.8 micra (dried smear); icteric index, 2; fragility of red blood cells, normal (B.H., 0.44 per cent; C.H., 0.34 per cent). Serum calcium, 8.9 mg.; serum phosphorus, 4.7 mg. Hinton test negative.

Gastric analysis with ergamin showed no free acid in 3 specimens. *Roentgenograms* of the lungs showed an old fracture of the ninth rib and changes consistent with mild silicosis. The heart was grossly enlarged to the right and left, predominantly in the region of the ventricles. The long bones were denser than normal and the medullary cavity definitely narrowed. The bone trabeculae were dense and closely packed.

Course. Following the above roentgenologic report, a bone marrow biopsy was done and the diagnosis of osteosclerotic anemia established.

Sternum. Microscopic examination shows numerous rather thick, closely spaced bony trabeculae. The intertrabecular spaces are occupied by dense fibrous tissue in which very rare scattered myeloblastic and hematopoietic cells are seen. There are scattered, ill-defined, multinucleated cells which are probably megakaryocytes. The findings are essentially similar to those of Case 1, the changes being slightly more marked.

The patient did not respond to liver and iron therapy and a low grade afternoon fever persisted while at rest in bed. Scattered petechiae continued to appear, but four blood cultures gave no growth. After two transfusions, 2 weeks apart, there was marked subjective improvement and he was discharged with red blood cells 2,100,000 per c.mm.

On July 5, 3 months later, he returned in much the same state as at first. In the interval he had followed instructions by taking 12 gm. of iron and ammonium citrate daily and had received three transfusions at his local hospital. All examinations were essentially as before except that the heart was decreased in size and the diastolic murmur had disappeared. The opinion was that this was an anemia heart without valvular disease. Reticuloocytes and immature white cells varied from 4 to 5 per cent. Intravenous and intramuscular aqueous liver extracts did not increase the red blood cell count above 2,100,000. A transfusion of 500 cc. was followed in 3 days by another of 250 cc., but for the remaining 6 weeks in the hospital he maintained the same low count.

Biopsy: Microscopic examination on bone marrow removed from the site of the original biopsy 6 months before shows a markedly different appearance. Bone trabeculae are still abnormally numerous and thick. There is a tendency to callous formation. The intertrabecular spaces are no longer occupied with cellular fibrous tissue but are so closely packed with cells that identification is difficult. The predominant cells are multinucleated osteoclasts. The remaining marrow is more fibrous than normal and contains many young, apparently proliferating fibroblasts. Packed in the interstices are clusters of stem cells and masses of myeloid elements, the eosinophilic myelocytes predominating. Transition forms between stem cells and mature red cells are almost wholly lacking.

On marrow removed from an adjoining area an estimation of the silica content by King's method gave the results shown in Table 2.

TABLE 2.—SILICA CONTENT OF BONE MARROW.

Mg. of SiO₂ per gm. of dried marrow.

Case 2	1.3
	1.2 (0.25 gm. dried marrow)
Normal	0.7
	0.4

Following this the patient was discharged home, subjectively improved but maintaining the same grade of anemia. When last heard from, on July 29, 1932, his status was unchanged and he was confined to a chair and bed life.

Comment. This type of osteosclerosis, termed myelosclerosis by Mozer, has been described in association with leukemia and with aleukemic or aplastic anemias. In 1879, in a young man dying of myeloid leukemia, Hueck found that the bone marrow was fibrous and traversed by a fine network of bony trabeculations. Schmorl, Sternberg and Mozer added like instances and Goodall described a case in an infant.

In a case without leukemia showing similar pathologic changes Askanazy demonstrated hemopoiesis within the widened capillaries of the liver and spleen. Since then in 14 cases* of myelosclerosis without leukemia, 11† showed evidence of compensatory myeloid metaplasia in the spleen. In 2 of the 11 cases^{18,24} death followed splenectomy. In all probability the enlarged liver and spleen in the 2 cases I have reported harbor active hemopoiesis. In the first case the adrenalin effect was interpreted as the result of shrinkage of a spleen rich in immature blood.

In many of the cases reviewed the diagnosis of aleukemic leukemia had been made because of the immaturity of the blood cells. Such immaturity is consistently reflected in these 2 additional cases by the decreased diameter of the red blood cells, the reticulated forms and the frequent myelocytes. Rather than a leukemic process, this appears to be the continued hurried response of an insufficient number of marrow cells. In both cases the red blood cells could not be maintained above 2,500,000. It seems that the maximum output of the reduced marrow tissue was equivalent only to this low level.

The future of these patients is quite uncertain, although it is known that Jores' patient lived as long as 8 years with the disease.

This type of osteosclerosis appears to be a response to injury rather than a metabolic disease, as is likely in marble bones. Subacute bacterial endocarditis was considered in the second case particularly because of the previous observation¹⁷ of the coexistence of these diseases. Similar but local reactive processes such as osteoplastic cancer metastases, "spotted bones,"²² radiation osteitis¹⁵ and periosteitis and sclerosis associated with phosphorus poisoning²⁶ were excluded. It is of some interest that marrow sclerosis has been produced in animals by strontium feeding¹¹ and by intravenous saponin.⁶

In these 2 cases there was a prolonged exposure to silica dust. No such exposure could be determined from the histories of the cases

* See Bibliography, Nos. 4, 7, 9, 11, 16, 17, 18, 21, 24, 25, 28.

† See Bibliography, Nos. 4, 7, 9, 11, 16, 17, 18, 24, 28.

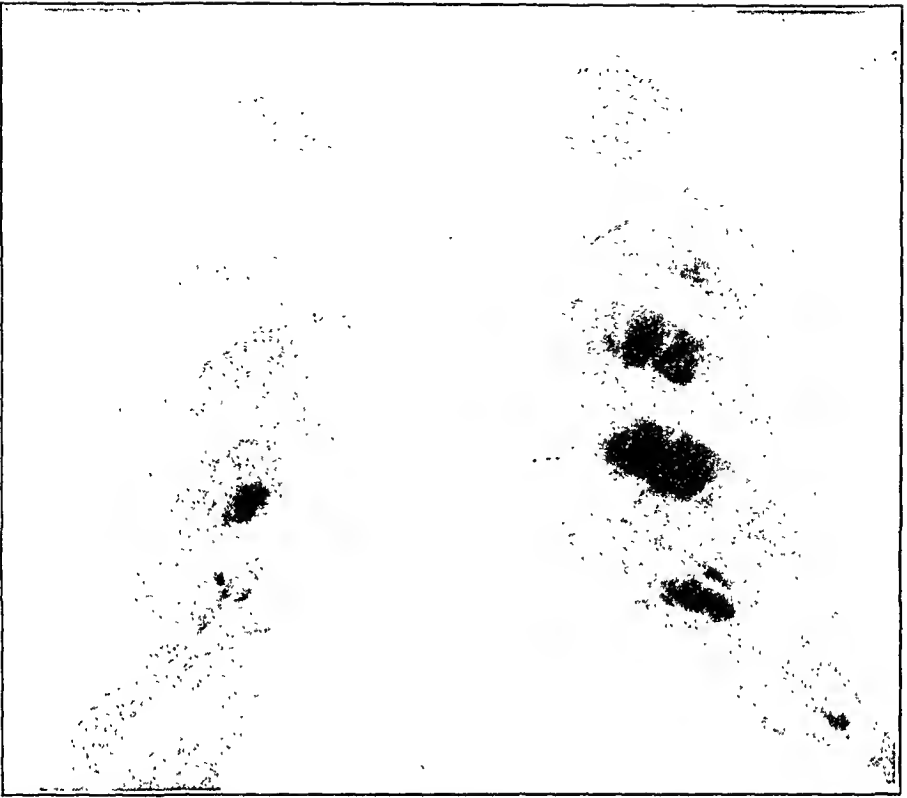


FIG. 1.—Case 2. Roentgenogram of the chest, showing an old fracture of the ninth rib and changes consistent with mild silicosis.

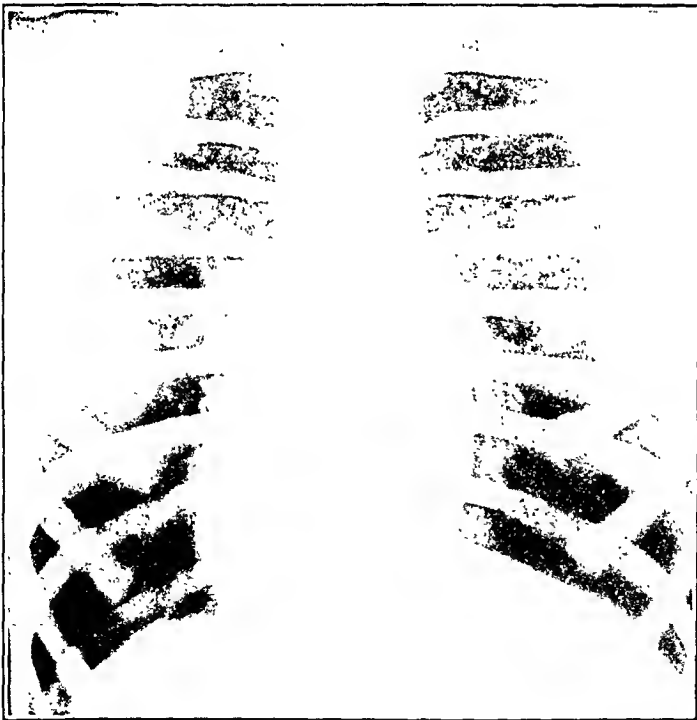


FIG. 2.—Roentgenogram of the chest of a child, aged 8 years, with marble bones. (Unpublished collection of Dr. C. N. McPeak.) Note the marked density of the bone with obliteration of the bony structure.

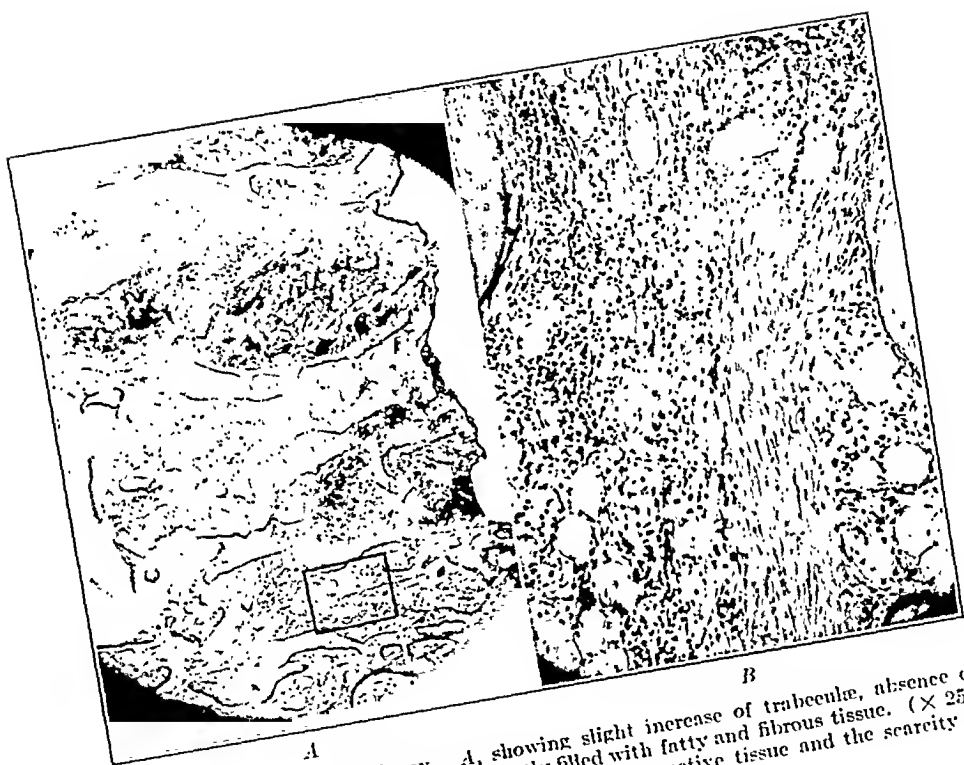


FIG. 3.—Case 1. Rib biopsy. A, showing slight increase of trabeculae, absence of osteoid tissue and interosseous spaces mostly filled with fatty and fibrous tissue. ($\times 25$.) B, from the area indicated in A. Note the dense connective tissue and the scarcity of marrow cells. ($\times 175$.)

reviewed, in most of which the origin of the disease is quite obscure. Welch has described multiple anthracotic nodules in the liver and more recently Riddell has found extrapulmonary silicosis in the liver and spleen. Although no such description has been found,* it is possible that cell ingested silica could be deposited in the marrow and there produce sclerosis. The estimations of silica in the marrow of the case with evidence of silicosis are interpreted as normal until more tissue is available. In 75 patients with moderate to advanced silicosis personally examined in Barre, Vt., in the past year none showed evidence of an osteosclerotic anemia.

Summary. 1. Two cases of unexplained osteosclerosis are presented. Fever, splenomegaly and a myelophthisic anemia with evidence in the peripheral blood of active hemopoiesis were the outstanding features.

2. The best treatment is palliative with transfusions, while splenectomy, arsenic and radiation are contraindicated.

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* Since submission for publication osteosclerosis associated with silicosis has been found in workers in cryolite. (P. F. Møller and S. V. Gadjonsson. *Acta Radiologica*, 1932, 13, 269.) In several a moderate anemia of secondary type was present but examination of the bone marrow was not reported. In these cases the sclerosis both of ligaments and bones was attributed to the sodium fluorid present in cryolite.

NEGATIVE RESULTS OF OXYGEN THERAPY IN POLYCYTHEMIA VERA.

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BERT¹ was the first to suggest that a lowered supply of oxygen to the body resulted in an increase in the oxygen-carrying capacity of the blood (1878, 1882). That an actual polycythemia resulted from ascent to high altitudes was demonstrated in 1889 by Viault,² whose erythrocyte count rose from 5,000,000 to 8,000,000 cells at an altitude of 4392 meters in the Peruvian Andes. Studies by Dallwig, Kolls and Loewenhardt³ and by Campbell⁴ on animals kept in low oxygen tensions but at normal barometric pressures showed that the degree of polycythemia produced was proportional to the severity of the anoxemia. Similar results were obtained in men breathing air containing low concentrations of oxygen.⁵ The occurrence of varying degrees of polycythemia as a result of anoxemia in clinical disease is seen in congenital heart disease, emphysema of the lungs and in chronic carbon monoxid poisoning.

As a result of the diminished rate at which gases (oxygen and carbon monoxid) passed through the lungs in 7 tested cases of polycythemia, Harrop and Heath⁶ suggested that an actual reduction in arterial blood oxygen tension might be present and might constitute the stimulus to the increased erythropoietic activity. Favorable results were claimed by Koranyi⁷ and Benes⁸ as a result of oxygen inhalations. Harrop⁹ mentions that 3 hours of oxygen inhalation produced no change in a case of his own and refers to an unpublished case of Binger and 1 of Poulton,¹⁰ in which no change resulted from the inhalation of 40 per cent oxygen for several days in an oxygen chamber.

The possibility that polycythemia vera might be an example of histotoxic anoxemia from an unknown poison interfering with the absorption of oxygen by the tissue cells led to a renewed trial of oxygen inhalation over a longer period of time. Barcroft, Hunt and Dufton¹¹ had showed that a reduction in red blood cells and hemoglobin took place after a week's exposure to 40 per cent oxygen in cases of chronic gas poisoning that had a relative poly-

cythemia. Campbell¹² and Barach¹³ reported that a slight diminution in erythrocytes and hemoglobin took place in normal animals exposed to 60 per cent oxygen over longer periods of time.

Two cases were selected from the ward service and put into an oxygen chamber of the Barach¹⁴ type for 15 days in 1 case and 17 days in the other. The oxygen concentration was maintained at 50 per cent. The temperature was between 68° and 70° F., the relative humidity 40 per cent.

The case histories and tables follow:

Case Reports. CASE 1.—R. I. (No. 326995), a Norwegian butler, aged 59 years, was admitted, January 11, 1932, complaining of shortness of breath and cramps in various parts of his body. His abdomen and legs were said to have been swollen for 5 months. He was aware of having had diabetes for 8 years. Attacks of substernal pain were sufficiently severe to suggest coronary disease. There were also cramplike pains in arms, shoulders and legs. He had attacks of dizziness and shortness of breath even when resting in bed.

On examination, the important findings were: an enlarged heart, systolic murmurs at the apex and aortic areas, with numerous premature beats. The liver edge was felt 4 cm. below the costal margin, but the spleen was never palpable. The lower extremities were edematous. Blood pressure was 160 systolic and 80 diastolic.

The blood count revealed polycythemia; red blood cells, 7,940,000 to 11,270,000; hemoglobin, 138 to 142 per cent. The urine contained both albumin and sugar. An electrocardiogram showed evidence of myocardial damage and fairly numerous extrasystoles. Roentgen ray of the gastrointestinal tract showed no evidence of organic disease.

The cramplike pains were the most annoying symptom. Nitroglycerin helped slightly but rarely afforded complete relief.

TABLE 1.—RESULTS IN CASE 1 BEFORE AND AFTER 17 DAYS' RESIDENCE IN A CHAMBER CONTAINING 50 PER CENT OXYGEN.

Date, 1932.	Hgb.	R.b.c.	W.b.c.	Polys.	Arterial oxygen content.	Oxygen capacity.	Arterial oxygen saturation.	Remarks.
Jan. 11	138	7,940,000	8,400	79				
13	142	11,270,000						
14	142	8,760,000	7,120	77				
15	142	8,760,000	7,120	77				
18	132	9,800,000	9,000	78	Phlebotomy, 500 cc.
27	145	9,500,000	9,300	81	Phenylhydrazin, 2 gm.; 2 days.
29	142	9,100,000	10,000	79	
Feb. 1	140	9,300,000						
4	138	8,100,000	10,800	80	Phenylhydrazin, 2 gm.; 2 days.
8	130	9,600,000						
10	129	8,400,000						
15	130	8,300,000	7,400	84	Entered oxygen chamber.
17	130	8,200,000	10,400	80	25.5	26.5	96.3	
23	120	8,000,000	9,500	83				
29	120	8,000,000	9,500	83				
Mar. 2	126	7,500,000	24.5	24.9	98.4	
4	126	7,500,000	Left oxygen chamber.

He was given a little phenylhydrazin hydrochlorid (0.8 gm. in 10 days) with no apparent benefit. He was put in the oxygen chamber, where he remained for 17 days. The cramplike pains were markedly diminished

in frequency and severity during the first 24 hours, and, although they recurred from time to time, were never as troublesome as before admission to the oxygen chamber.

The erythrocyte count, hemoglobin percentage and oxygen capacity are seen in Table 1 to be uninfluenced by residence in an oxygen-rich atmosphere. The arterial oxygen saturation was slightly increased when he was breathing 50 per cent oxygen.

CASE 2.—T. B. (No. 329295), a man, aged 48 years, entered the ward with a 6-month's history of noises in head, dizziness and shortness of breath. Two years before admission he had vomited blood several times. Headaches were annoying at this time but improved as he lost weight. During the past 2 years his weight had dropped from 230 to 173 pounds.

He had received two courses of treatment with phenylhydrazin 9 months before admission (2 gm. in 2 months). Three months before admission he had taken 1.6 gm. in 2 weeks. The red cells dropped from 11,000,000 to 7,700,000 but subjective improvement was not marked.

When admitted, the patient was a large, plethoric and cyanotic Italian, apparently chronically ill. The heart was enlarged, but the sounds were of good quality and no murmurs were heard. The blood pressure was 110 systolic and 70 diastolic. The right lung was apparently normal. At the left base there was slight dullness, with diminished voice and breath sounds. The spleen was felt 4 cm. below costal margin. The liver was not palpable. In the left upper quadrant there was a large, freely movable, nontender mass, approximately 10 cm. in diameter. This was thought to be kidney but Roentgen ray threw no light on the subject and its actual nature remained in doubt.

The patient was placed in the oxygen chamber for 15 days with little change in symptoms or blood count. The arterial oxygen saturation was very slightly below the usual normal range before he entered the chamber. It increased from 93.2 to 98.3 in 50 per cent oxygen.

One month later he seemed to feel a little better and the red cells were a trifle lower.

TABLE 2.—RESULTS IN CASE 2 BEFORE AND AFTER 15 DAYS' RESIDENCE IN A CHAMBER CONTAINING 50 PER CENT OXYGEN.

Date.	Hgb.	R.b.c.	W.b.c.	Polys.	Arterial oxygen content, vol. %.	Oxygen capacity, vol. %.	Arterial oxygen saturation, vol. %.	Remarks.
Feb. 10	115	8,000,000						
14	125	7,550,000	17,400	95				
16	127	10,300,000	22,300	82	23.1	21.5	93.2	
17	Entered oxygen chamber.
23	135	9,500,000	17,200	84				
29	122	9,000,000	17,300	84				
Mar. 1	122	23.5	23.9	98.3	
4	122	8,700,000	Left oxygen chamber.
29	115	8,200,000	29,600	85				

Summary. No significant alteration in the red blood cell count, the hemoglobin percentage or the oxygen capacity took place in either of 2 cases of polycythemia vera who breathed an atmosphere containing 50 per cent oxygen for a period exceeding 2 weeks. This appears to make improbable the theory that polycythemia vera is based on an anoxemic stimulus. The relief of the cramp-

like pains in 1 case seemed due to an alleviation of a condition of local anoxemia associated with the presence of an increased number of red cells and a consequent locally retarded blood flow. In each of the cases there was a slight increase in the arterial oxygen saturation while the patients were breathing 50 per cent oxygen in the chamber.

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ANEMIA IN AZOTEMIA.*

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ANEMIA is common in chronic nephritis. Richard Bright¹ observed its development in the course of the disease, remarking, "After a time the healthy colour of the countenance fades." That anemia may occur in various renal lesions other than chronic glomerular nephritis, such as nephrosclerosis, polycystic kidneys, failure of one kidney following the surgical removal of the other, and in renal damage resulting from urinary retention due to hypertrophy of the prostate, is less commonly recognized. From a review of the liter-

* Read before the Section on Pathology of the California State Medical Association, April 28, 1931.

ature and case studies we shall show the parallelism that exists between the anemia and the nitrogen retention (azotemia), not only in chronic Bright's disease, but in other pathologic renal conditions.

Robert Christison² was among the first to make accurate analysis of the blood in chronic nephritis. He well understood the grave prognostic significance of the gradually developing anemia, stating, ". . . the proportion of the hematosin in the blood has appeared to me to constitute under certain conditions one of the surest criterions of the progress which the organic derangement has made in the structure of the kidneys, and therefore to be one of the most useful symptoms which a physician can attend to in a practical point of view" (loc. cit., p. 31). The "hematosin," or "the coloring matter" of the blood was determined by allowing the corpuscles to settle out in a weighed sample of defibrinated blood and determining their dry weight in proportion to the total weight of the original sample of blood. The amount of hematosin in healthy adults varied, according to Christison, from 1160 to 1535 parts per 10,000 of blood. From a table (p. 35) in which are recorded 10 cases of "granular kidney," the amount of hematosin varied from 1339 (normal) to as low as 427, with an average of 905.3 parts per 10,000 parts of blood, or about 67 per cent of the normal figure (obtained by averaging 1160 and 1535, given above).

In 1850, Schmidt,³ studying the blood of cholera patients, also included in his report several (loc. cit., pp. 111, 121, 127) cases of nephritis. He found in them a marked decrease in the volume of the cells in proportion to the plasma. An example (p. 127) was a man aged 39 years, with chronic nephritis and marked edema. The blood contained 34.2 per cent cells and 65.7 per cent plasma by volume—a considerable degree of anemia. In 1878, Leichtenstern⁴ demonstrated a reduction in the amount of hemoglobin in Bright's disease. He studied the blood in 3 chronic cases and found that the hemoglobin content was ". . . appreciably reduced, in a high degree particularly in a case of 'granular atrophy' of the kidneys with a waxy-yellow appearance of the patient" (p. 88; also Table 19, pp. 90, 91). In this case the hemoglobin was 9.22 gm. per 100 cc. of blood (by calculation based on spectrophotometric figures in the text).

The cause of the anemia in azotemia is still unknown. In 1905, Ceconi⁵ made careful studies on the blood in 25 cases of nephritis. He found no increase in the fragility of the erythrocytes, but rather, in general, a tendency to an increased resistance. This he attributed to some retained toxic substance which rendered the union between the hemoglobin and the erythrocyte more tenacious. He concluded that the anemia in chronic nephritis was not due to increased red cell destruction, but rather to a deficiency in the hematopoietic system, which was probably caused by a paralyzing action of retained poisons.

Grawitz⁶ was of the opinion that the blood plasma became richer in water, that is, hydremic. He recognized two stages in the course of chronic nephritis. First, a stage of adequate cardiac function with no alteration in concentration or number of erythrocytes in the circulating blood; later, a stage of inadequate cardiac function due to weakening of the hypertrophied left ventricle of the heart. In this stage he said, ". . . there is a progressive thinning of the blood due to the increase in water . . ." leading to ". . . abnormally lowered values for the blood corpuscles and hemoglobin."

This dilution theory has been disproved by the work of Keith, Rowntree and Gcraghty⁷ in 1915. Studying the relationship of the plasma volume to the total blood volume they found that the latter constitutes 1/11.4 of the body weight and that the former varies from 42 to 56 cc. per kg. of body weight. They also observed that the plasma volume was not increased in chronic nephritis. This work has been confirmed by Bock.⁸ He found that the blood plasma constitutes 5.1 per cent or 1/19.6 of the body weight, and that it remains remarkably constant both in health and disease. In cases of edema in cardiac and renal disease he found the plasma volume remained constant.

From the observations of these workers it is evident that no increase in total plasma volume occurs in chronic nephritis. Therefore, the anemia which is usually present in the advanced stage of the disease is not due to simple dilution of the corpuscles, but rather to an absolute decrease in their number.

Fundamentally, there are three types of anemia: (1) Anemia due to deficient blood formation; (2) anemia due to excessive blood destruction, and (3) anemia due to blood loss. The amount of blood lost in the urine in chronic nephritis is probably too small to account for the anemia. Brown and Roth⁹ found that in 89 cases of chronic nephritis with anemia, 34 (38 per cent) showed no erythrocytes in the urine, although the hemoglobin averaged 59 per cent and the erythrocytes 3.01 millions per c.mm. of blood. Furthermore, no relationship was found to exist between the amount of blood in the urine (excluding its presence macroscopically) and the degree of anemia. For example, 4 cases, with sufficiently large amounts of blood to be almost macroscopic, had an average hemoglobin of 57 per cent and erythrocyte count of 2.95 millions, while 39 with almost no blood microscopically visible had averages of 54.7 per cent hemoglobin and 3.31 millions erythrocytes.

The problem of the rôle of excessive destruction of blood in the body in the pathogenesis of anemia in chronic nephritis is not so easily settled. Clark and Evans¹⁰ showed that the serum of patients having pernicious anemia exhibits a decrease in its protective anti-hemolytic property. Experiments were conducted *in vitro*, using guinea-pig erythrocytes and sodium oleate for the hemolytic agent. A marked decrease in protective antihemolytic power of pernicious

anemia serum as compared with serum from normal subjects and those suffering from a wide range of diseases without anemia was observed. While some reduction in protective power of the serum was observed in various other types of anemia, it was much less than in pernicious anemia.

Brown and Roth⁹ tested the protective value of the blood serum against hemolysis of homologous erythrocytes by hypotonic salt solution and found that the protective property of human serum is fairly constant in both normal persons and those suffering from chronic nephritis, either with or without anemia.

The chief underlying factor in the pathogenesis of anemia in chronic nephritis is probably defective blood formation. The appearance of the erythrocytes in stained smears lends support to this hypothesis. Anisocytosis, poikilocytosis, polychromasia and hypochromasia were not at all marked in the slides of our cases. Nor was the color index very low as in other secondary anemias (Table 3). Brown and Roth⁹ found no increase in the reticulocytes in a number of their cases, even though the anemia was quite severe. While most writers refer to the anemia in chronic nephritis as "secondary," it is not markedly hypochromic. In fact, there seems to be an element of aplasia of the marrow involved. More careful studies of the bone marrow are needed in this field.

Some authors have reported examples, in their opinion, of hyperchromic anemia in chronic nephritis. Berg¹¹ observed that in 7 of his 12 cases (Table 1) of chronic nephritis with nitrogen retention the color index was 1 or slightly above, as 1.1. From a study of our cases (Table 3) we have found a similar circumstance, but we do not regard it as evidence of hyperchromia but rather of a high normal reading. For routine work we use the new Sahli hemoglobinometer, carefully checked against the Bausch & Lomb Company's Newcomer type instrument. The latter has been very carefully calibrated by us, using the O₂ and CO₂ combining power methods. Only very slight readjustment was found necessary. An average color index of 1.31 has been found in 76 cases of pernicious anemia carefully studied by us in the hematology laboratory since August, 1930. In normal individuals we usually find the color index 0.9 to 1. The enumeration and morphology of the leukocytes in the anemia of chronic nephritis have been insufficiently studied. In 20 of our cases, including 1 of polycystic kidneys, we found an average white cell count of 13,839, which is considerably higher than the average of 9020 in the 105 cases reported by Brown and Roth.⁹ We frequently observed a moderate shift to the left in the neutrophils in our cases, but this may have been due to terminal complicating infections which, in turn, may be the reason we so commonly found a mild leukocytosis.

Kollert and Paschke¹² observed that infections complicating nephritis, as sinusitis, tonsillitis, endocarditis and otitis media, pro-

duced an alteration in the leukocytic picture with a leukocytosis and a shift to the left in the neutrophils. These changes coincided with an increase in the sedimentation rate of the erythrocytes. Schilling¹³ states that there is little or no shift in uncomplicated cases of chronic nephritis.

The blood platelets in some cases of chronic nephritis are reduced in number. Brown and Roth⁹ found an average of 152,000 per c.mm. in 8 of their cases. "A condition," they remarked, "which may have some bearing on the hemorrhagic tendency in some of the more severe cases of chronic nephritis with anemia." We have not found a material reduction in their number in our cases. In fact, Case 16 (Table 3) is that of a young woman having very severe bleeding from the gums, which was the outstanding clinical feature until further study proved the existence of chronic nephritis, and yet the platelet count was 274,000. Case 21 was very similar, but unfortunately no platelet count was made.

The relationship of nitrogen retention to anemia is very important. From a review of the literature it appears that the anemia is not limited to cases where the retention is due to chronic nephritis, but is also seen in azotemia due to other lesions, as congenital polycystic kidneys, arteriosclerotic renal disease, surgical removal of one kidney with failure of the other, and in urinary retention due to hypertrophy of the prostate.

Aubertin and Yacoel¹⁴ in their article, presented a table (p. 462) which included 11 cases of chronic nephritis with azotemia and 6 cases without azotemia. The average total nonprotein nitrogen (our calculation) in the azotemic group was 244 mg. per 100 cc. of blood; the average number of erythrocytes, 2.46 millions per c.mm. In the nonazotemic group the nonprotein nitrogen averaged 43 mg. and the erythrocytes 3.66 millions. They concluded that in nephritis with azotemia there is a severe anemia, while those cases without nitrogen retention showed an insignificant anemia. Berg,^{11,15} in 1922, in a study of 28 cases of nephritis, 12 of them with nitrogen retention ranging from 43 to 214 mg. of urea per 100 cc. of blood, found that severe anemia in chronic nephritis is seen chiefly in cases with nitrogen retention. However, 1 of his cases with only 50 mg. of urea had 1,504,000 red blood cells, while another with 121.8 mg. of urea had a red count of 4,180,000. Brown and Roth⁹ in the same year, in an analysis of 187 cases of chronic nephritis, of which 105 had anemia, concluded that anemia was not proved to be due to an increase of nitrogenous substances in the blood, although if severe, had the same prognostic significance as creatinin retention. They observed that hemoglobin values of 60 per cent or less have approximately the same serious prognostic significance as creatinin values of 5 mg. and above, over a 2½-year period. The same workers¹⁶ in the following year published a report on the prognostic value of anemia in chronic nephritis. Twenty of their cases had an average

hemoglobin of 48.5 per cent (Dare) and 2,950,000 red cells with creatinin of 5 mg. or above. Nineteen of these 20 died within 10 months of the time of first observation.

In 1924 Aubertin and Yacoel,¹⁷ from a study of 14 cases of chronic nephritis with nitrogen retention, concluded that the anemia that so often occurs in these cases is usually progressive and parallel to the azotemia. From our analysis of their cases we find that the average nonprotein nitrogen values in the blood were 185 mg. per 100 cc. of blood, and the red cell count 2.5 millions per c.mm. In studying the blood in cases of hypertension, Adams and Brown¹⁸ have observed that 56 cases with adequate renal function (normal urea and creatinin) had an average hemoglobin of 106 per cent and an erythrocyte count of 4,670,000. In the same study 20 cases with impaired renal function (nonprotein nitrogen above 50 and creatinin above 2.5) had an average hemoglobin of 81 per cent with 3,870,000 red cells. They stated that, "The anemia in cases of hypertension is not as marked as that observed in cases of glomerulonephritis." Furthermore, "Renal insufficiency can be recognized by the onset of anemia in cases of hypertension." The high normal and increased erythrocyte count in cases of hypertension has been designated by Geisböck¹⁹ as "polycythemia hypertonica." It is apparently not due to alterations of the blood volume or plasma volume, but may be due to compensatory erythropoiesis due to diminished oxygenation from varying degrees of cardiac insufficiency.

Scarlett,²⁰ in 1929, analyzed 51 cases of chronic nephritis and found as averages: erythrocytes, 2,780,000; hemoglobin, 51 per cent; color index, 0.9; urea nitrogen, 86.3 mg.; and creatinin, 9.3 mg. per 100 cc. of blood respectively. He agreed with the findings of other observers that the presence of a severe anemia in chronic glomerular nephritis has practically the same prognostic value as blood creatinin of 5 mg. or over. He also reported 4 cases of chronic glomerular nephritis with uremia without hypertension, cardiac hypertrophy or retinal changes, in which anemia was the only clinical finding. Three of these died within a year from the time first seen. All had increased blood nitrogen and a severe secondary anemia.

Ashe,²¹ in an excellent review of 300 cases of Bright's disease, myocardial insufficiency, hypertension, polycystic kidneys and surgical removal of one kidney, concluded that a secondary anemia is always present in renal insufficiency from any cause and is directly proportional to the degree of insufficiency. While the blood chemistry and renal function dye excretion tests are largely absent it is obvious from his study that the cases which he designated as showing "marked and maximal renal insufficiency" showed a definite anemia of the secondary type. Among this class 40 cases diagnosed by him as chronic diffuse nephritis showed an average hemoglobin of 54 per cent; red cells, 2,944,000, and a color index of 0.92. Those of renal insufficiency accompanying hypertension with maximal renal impair-

ment showed an average hemoglobin of 65 per cent; average red cells, 3,775,000, and a color index of 0.87. His study of 3 cases of polycystic kidney is valuable, although here again specific values for the blood chemical constituent and dye excretion tests are lacking. The first case showed a hemoglobin of 80 per cent and 4,256,000 red cells, and was classed as having moderately impaired renal function. The other 2 cases showed a hemoglobin of 44 per cent and 55 per cent and 2,728,000 and 3,900,000 red cells, respectively. These were designated as having maximal renal insufficiency. Two examples were also given of surgical removal of one kidney, one with no impairment of renal function with a hemoglobin of 80 to 90 per cent, the other with maximal renal insufficiency with a hemoglobin of 45 to 56 per cent and 2,500,000 to 3,882,000 red cells.

Van Slyke²² is in agreement with many others that the prognostic value of anemia is usually of the same weight as the increase in blood urea. He stated that although anemia is practically always present in the terminal stage of chronic nephritis, the absence of a low hemoglobin does not mean that uremia will not ensue. He found that anemia was present in arteriosclerotic Bright's disease in 5 out of 6 cases studied, but "to a less extensive degree than in the terminal cases of hemorrhagic nephritis" (glomerulonephritis). Further, that "anemia likewise is by no means uniformly absent in nephrosis." Out of 10 cases only 3 showed hemoglobin above 80 per cent. Also that "a blood hemoglobin content was also followed, and although of not decisive diagnostic value was found to be of interest as an indication of the toxic damage suffered by the organism, and to have prognostic significance."

Klemperer and Otani,²³ in a comprehensive study of 16 cases of nephrosclerosis, happily included hemoglobin and erythrocyte estimations of nearly all the cases. Excluding Case 1, a male, aged 29 years, blood pressure 230 systolic and 172 diastolic, with the urea 14 mg. and hemoglobin 102 per cent, 4,800,000 red cells, and Cases 5, 7 and 10, in which no record of blood counts or hemoglobin is given, we find the following averages: Urea, 84.5; hemoglobin, 53 per cent; 3,055,000 red cells; color index, 0.88. Lowest urea, 29; hemoglobin, 50 per cent; highest urea, 190; hemoglobin, 39 per cent. Lowest hemoglobin, 35 per cent; urea, 45; highest hemoglobin, 70 per cent; urea, 63. Lowest red cells, 1,250,000; urea, 45. Highest red cells, 4,600,000; urea, 63. From these last figures it is at once obvious that the functional status of the hematopoietic system varies markedly in individual cases and is not an exact indication of the degree of nitrogen retention. On the other hand, the average case with urea 84.5 had a definite secondary anemia.

In Table 1 we have summarized the figures of the various authors, including ourselves, who have reported series of cases presenting anemia with azotemia. It can be seen at a glance that there is a definite anemia in all the series. Unfortunately, it is impossible

accurately to compare the blood chemistry findings with these, since some authors have reported total nonprotein nitrogen values, others the urea, others creatinin, and one author stated that there was marked and maximal renal impairment without reporting the blood chemistry findings.

TABLE 1.—ANEMIA IN NITROGEN RETENTION (AVERAGE FIGURES IN LITERATURE).

Author.	Year.	No. of cases.	Blood chemistry.	Hb., per cent.	Erythrocytes, millions.	Color index.	Condition.
Aubertin and Yacoe ¹⁴	1920	12	N.P.N. 220	35	1.100	1.6	Nephrosclerosis
Berg ¹⁵	1922	12	Urea 92.5	47	2.550	0.93	Chronic nephritis
Brown and Roth ¹⁶	1922	20	Creatinin 8.8	48	2.950	0.82	Chr. glom. nephritis
Aubertin and Yacoe ¹⁷	1924	18	N.P.N. 112	..	3.270	..	Chronic nephritis
Adams and Brown ¹⁸	1925	20	N.P.N. (?) over 50	81	3.870	1.0	Hypertension with impaired renal function
Scarlett ¹⁹	1929	51	Urea 86.3	51	2.780	0.90	Chronic nephritis
Ashe ²¹	1929	10	*	54	2.940	0.92	Chr. diffuse nephritis
Ashe	1929	18	*	65	3.377	0.87	Hypertension with impaired renal function
Ashe	1929	2	*	49	3.310	0.74	Polycystic kidneys
Ashe	1929	1	*	50	3.190	0.80	Surg. remov. of 1 kidn.
Klemperer ²²	1931	15	Urea 84.5	53	3.055	0.88	Malign. nephrosclerosis
Parsons and Ekola-Strolberg	1931	2	N.P.N. 250	53	2.390†	1.0†	Congenital polycystic kidneys
		2	Creatinin 6.5	53	3.265	0.93	Acute nephritis
		4	N.P.N. 176	55	2.672	0.91	Nephrosclerosis
		4	Creatinin 5.6				
		13	N.P.N. 218	50.7	2.578	0.99	Chr. glom. nephritis
			Creatinin 9				
			N.P.N. 193				
			Creatinin 8.3				

* Marked and maximal renal impairment.

† One case only.

TABLE 2.—NORMAL CREATININ VALUES BELOW 5 MG. PER 100 CC. OF BLOOD.

Number.	Laboratory number.	Age.	Sex.	Renal lesion.	Duration of symptoms.	Nonprotein nitrogen.	Creatinin (mg. per 100 cc.).	Erythrocytes (millions).	Hemoglobin (per cent).	Color index.	Leukocytes.	Platelets (thousands).
1	H-210	63	M	Nephrosclerosis	2 mos.	40	1.3	3.89	77	1.0	8,350	
2	H-215	31	M	Amyloid nephr.	1 yr., 4 mos.	30	1.5	4.00	96	0.98	10,950	
3	H-261	28	M	Acute nephr.	2 mos.	41	1.5	3.76	84	1.12	17,800	328
4	H-287	72	M	Prostatism	60	1.5	5.11	97	0.95	25,150	152
5	H-275	51	M	Chr. glom. neph.	80	1.5	3.95	83	1.05	9,600	291
6	H-670	13	F	Subacute glom. neph.	8 mos.	50	1.6	2.42	37	0.77	7,000	370
7	H-323	60	M	Embolie neph.	Few weeks	82	1.7	5.00	108	1.08	7,850	172
8	H-208	40	F	Pyelonephritis	2 mos.	29	1.8	3.51	71	1.0	14,550	144
9	H-495	69	M	Arterioscl. neph.	3 wks.	78	2.0	4.89	89	0.92	7,250	200
10	H-558	42	M	Bilat. ren. calc. w. pyeloneph.*	1 mo. with N.P.N. above 50	85	2.1	4.97	99	1.01	15,650	236
11	H-219	37	M	Chr. glom. neph.	1 yr., 3 mos.	96	2.1	6.25	116	0.93	14,550	220
12	H-553	55	F	Bilat. ren. calc. w. pyeloneph.*	1 wk. with N.P.N. above 40	133	2.3	4.65	91	0.97	37,600	
13	H-405	85	M	Prostatism	Few days	109	2.4	4.76	91	0.96	11,650	190
14	H-384	20	F	Nephrosclerosis	10 mos.	150	2.6	2.57	43	0.86	9,950	431
15	H-506	27	M	Prob. nephroscl.	1 yr. intermit.	125	3.0	3.69	80	1.1	9,950	178
16	Autop. 2126	44	M	Chr. glom. neph.	3 mos.	120	3.0	3.80	70	0.92	12,050	
17	H-502	35	M	Chr. glom. neph.	4 yrs. intermit.	100	3.2	3.21	69	1.07	6,150	216
18	Autop. 4951	78	M	Arterioscl. neph. ren. chl.†	N. retention about 6 mos.	133	3.3	4.60	95	1.03	8,900	
19	H-475	56	M	Malign. nephroscl.	3 mos.	98	3.5	2.90	63	1.08	10,450	203
20	H-507	67	M	Nephrosclerosis	2 yrs.	133	4.0	2.77	59	1.09	11,750	135
21	H-619	62	M	B. pyonephrosis, 1 kidney out.	3 yrs.	150	4.7	2.10	42	1.0	4,550	250
Averages:						2.4	3.09	74	0.95	11,385		

* Bilateral renal calculi with pyelonephritis.

† Arteriosclerotic nephritis with renal calculi.

In Table 2 we have listed 21 cases of different types of renal lesions having creatinin values ranging from normal to 4.7 mg. per 100 cc. of blood. In only 2 of these was the creatinin above 3.5 mg., although the nonprotein nitrogen showed figures as high as 150 mg. The average creatinin was 2.4 mg.; erythrocytes, 3,988,000; hemoglobin 74 per cent, and the color index, 0.95.

In Table 3 are 21 examples of renal lesions with creatinin values ranging from 5 to 12 mg. per 100 cc. of blood. These cases have been classified according to the lesion in Table 1 and the average figures for the different lesions recorded there. The average creatinin in these 21 cases is 7.6 mg.; erythrocytes, 2,570,000; hemoglobin, 52.5 per cent, and the color index, 1. It may be seen that a very considerable degree of anemia is present in these cases. Case 4 is an apparent discrepancy having a creatinin 5.3 and 4,390,000 red cells, the duration of symptoms, however, was only 15 days and it is not unlikely that, had the azotemia persisted over a longer period of time, anemia would eventually result.

TABLE 3.—CREATININ VALUES OF 5 MG. OR ABOVE PER 100 CC. OF BLOOD.

Number.	Laboratory number.	Age.	Sex.	Renal lesion.	Duration of symptoms.	Nonprotein nitrogen.	Creatinin (mg. per 100 cc.).	Erythrocytes (millions).	Hemoglobin (per cent).	Color index.	Leukoocytes.	Platelets (thousands).
1	H-401	40	F	Nephrosclerosis	6 mos.	300	5.0	3.41	58	0.85	17,450	324
2	Autopsy 2262	45	F	Chr. glom. neph.	Over 1 yr.	200	5.0	2.33	50	1.0	20,000	
3	H-667	34	F	Chr. glom. neph.	4 mos.	200	5.3	3.15	62	1.0	20,900	
4	H-332	23	F	Acute nephritis	15 days	153	5.3	4.39	75	0.87	11,900	382
5	H-474	55	M	Nephrosclerosis	6 mos. (?)	162	6.0	3.23	71	1.1	15,750	152
6	Autopsy 2245	40	M	Chr. glom. neph.	2 mos.	120	6.0	2.94	70	1.2	19,200	
7	Autopsy 3850	51	F	Chr. glom. neph.	12 yrs.	143	6.0	3.50	63	0.9	8,800	
8	Autopsy 7303	42	F	Congen. cyst. kidneys	5 mos.	260	6.0	2.39	46	1.0	13,550	304
9	H-391	27	F	Acute nephritis	3 mos.	200	6.0	2.14	42	1.0	12,050	292
10	Autopsy 5086	69	F	Chr. glom. neph.	4 mos. (?)	122	6.2	2.90	40	0.68	19,000	
11	Autopsy 7417	44	M	Congen. cyst. kidneys	3 mos.	240	7.1	...	60			
12	H-222	52	M	Nephrosclerosis	1 yr.	171	7.5	1.91	37	0.97	13,150	372
13	H-221	35	M	Chr. glom. neph.	2 mos.	214	8.5	1.35	25	0.96	21,000	508
14	Autopsy 4675	48	M	Nephrosclerosis	1½ yrs.	240	8.6	2.14	5,950	
15	Autopsy 5428	40	M	Chr. glom. neph.	3 mos. (?)	200	8.6	3.00	20,400	
16	H-622	23	F	Chr. glom. neph.	2 mos.	187	9.1	1.38	26	1.00	10,250	274
17	H-465	26	M	Chr. glom. neph.	2 yrs.	184	9.3	1.92	32	0.81	7,800	
18	Autopsy 7895	52	F	Chr. glom. neph.	6 wks.	200	10.0	2.80	40	0.70	14,750	
19	Autopsy 3498	37	M	Chr. glom. neph.	1 mo.	250	10.0	3.14	90?	1.4?	10,440	
20	Autopsy 3490	46	M	Chr. glom. neph.	3 mos.	240	12.0	3.51	85	1.2	10,450	
21	Autopsy 5023	36	F	Chr. glom. neph.	1 mo. (?)	254	12.0	1.60	26	0.81	11,000	
Averages:	7.6	2.57	52.5	1.05	13,839	

From the series of cases reported and tabulated in Table 1, as well as from our own study, it is apparent that anemia is an almost constant accompaniment of azotemia. Whether the nitrogenous

substances retained in the blood are the cause of the anemia or not is an open question. Other organic and inorganic compounds are also retained in the blood plasma in renal insufficiency, as for example, indican reported by Monias and Shapiro²⁴ and inorganic sulphates reported by Wakefield, Power and Keith.²⁵ The consensus of opinion seems to be that the anemia is the result of a depressed activity of the hemopoietic tissues. Just what substance or substances or, perhaps, toxin may be the ultimate causative factor in the production of anemia remains to be discovered. The close parallelism between azotemia and anemia, however, is very apparent, so much so, in fact, that hemoglobin values around 50 per cent have the same prognostic significance as creatinin values of 5 mg. or more.

Summary. 1. Anemia is almost constantly found in cases of azotemia regardless of the pathologic basis for the renal insufficiency.

2. The anemia is probably due to depressed activity of the hematopoietic tissues.

3. The specific etiologic factor in the production of anemia, if it be a single one, is not known.

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A STUDY OF THE CLASMATOCYTES IN THE SACROSPINALIS MUSCLE OF THE RABBIT.

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THE mononuclear phagocytic cells of the animal organism may be arranged in two rather indefinite components of the reticulo-endothelial system. Of these the fixed components of the system largely localized in the liver, spleen and bone marrow are often designated reticuloendothelial cells, whereas the migratory or wandering cells, present in every organ of the body, are perhaps best known as clasmatocytes. These wandering phagocytic cells are widely known to the cytologist, and their origin and morphology have been a favorite subject for study, but their functions are not so thoroughly understood by the surgeon and clinician. And yet injury to tissue of one sort or another, abrasions, contusions and surgical wounds, all induce a response by local clasmatocytes which contribute toward the process of recovery. Cellular exudates, either of the pleura or peritoneum, after the third day are practically exclusively clasmatocytic, and their contribution to the formation of fibrous tissues is quite generally recognized.

Although opinions to the contrary maintain, there are experimental data which lead one to conclude that these two systems of cells are not wholly independent of one another. The desquamation and migration of the fixed phagocytes of the liver and their subsequent identification as clasmatocytes is indicative of the opinion that considerable identity between the fixed and the wandering components of the reticuloendothelial system does exist. Such identity was sustained in the work of de Haan and Hoekstra. These authors concluded from perfusion experiments in rabbits that the reticular cell of the liver was identical to the mononuclear cells of a peritoneal exudate. The reaction of connective tissue to foreign irritants has long been a popular field for studies on cellular relationships. Although the literature on the origin, identity and function of these cells is enormous, there is an apparent lack of unity in the interpretation of results. Ekola has given an excellent review of the literature on the clasmatocyte, polyblast and fibroblast, so that any consideration at this time is unnecessary.

Clasmatocytes from various regions of the body, the peritoneum, pleura, omentum, mediastinum and subcutaneous spaces, have been studied with respect to their origin and their function, but we know of no study on the intramuscular reaction to an irritant.

Throughout this study we have considered the possible sources for the origin of these mononuclear phagocytes as well as their function and subsequent transformation.

According to Sabin, Doan and Cunningham the clasmatoocyte of animal tissue has a definite cytoplasmic organization which reacts in a characteristic way to supravital stains. It differs from the monocyte, which displays a definite rosette formation in the arrangement of its cytoplasmic granules. Clasmatoocytes are remarkably phagocytic and engulf huge quantities of any foreign material. This tendency has rendered them readily visible so that subsequent changes or transformations may be easily followed. By this means Hetherington followed the changes which occurred in the transformations of clasmatoocytes and monocytes into epithelioid cells and into giant cells. It is probable that epithelioid cells of pulmonary tubercles arise from the local wandering clasmatoocytes which mobilize so rapidly in the presence of any foreign body. The observations of Bloom, in which the transformation of lymphocytes and polyblasts into fibroblasts was seen, is supported by many observations in our laboratory wherein dye-laden mononuclear cells have displayed fibroblastic potencies.

Method. The sacrospinalis muscle of the rabbit, one of the most powerful muscles in the body, was selected as the site for the injections. The hair covering this region was removed and the skin washed and bathed with alcohol. After blocking a portion of the area with procain, 0.5 cc. of a graphite preparation was injected directly into the muscle. The tip of the needle was inserted deep enough to approximate the neural arch of the second lumbar vertebra, and the injection was made as the needle was slowly withdrawn. Ten animals were thus injected and they were killed at intervals ranging from 1 hour to 1 month later. The muscle which had been injected was excised at necropsy, fixed and stained with routine selective stains.

Observations. Inflammation was already manifest in sections of the muscle taken 1 hour after injection. This is in accord with prevailing opinion that decided signs of inflammation may be apparent 30 minutes to 1 hour after the injection of an irritant. Diapedesis had occurred and the graphite mass, together with erythrocytes, neutrophils and monocytes, was enmeshed in a fibrin network. Comparable cells were identified in the adjoining capillaries and there was every indication that the cells of the inflammatory lesion were derived from the blood stream, an observation first described about 70 years ago and since verified by numerous investigators.

At 3 hours after an injection there was tremendous engorgement of capillaries, and neutrophils and monocytes were seen migrating through the endothelium into the interfascicular spaces. Erythro-

cytes, lymphocytes, and monocytes were encountered with the neutrophils within the periphery of the graphite clump, and considerable phagocytosis by the neutrophils had occurred. At 6 hours a few large mononuclear cells, differing from those derived from the blood stream, were encountered in the sections. These were of histogenous origin and we believe were local clasmatoocytes or macrophages of the region. Occasional graphite granules were seen in blood monocytes and clasmatoocytes, yet phagocytosis at this time was far more active in the neutrophils.

The latter half of the 1st day and the 2d day were marked by an abundant proliferation or increase in the number of clasmatoocytes. Capillaries remained congested and the preponderant white cell within these fixed vessels was the monocyte. The neutrophils, so numerous during the first day, were disappearing, degenerating and they were phagocytosed by the mononuclear cells during the 2d and 3d days. Monocytes, bearing graphite granules, were seen in the fixed capillaries, and it was clear that these phagocytic agranulocytes had reentered the blood stream from the inflamed area. After the second day the mononuclear cells were the only active constituent, and the further resolution and organization of the lesion was purely a function of these nongranular leukocytes of the blood and the macrophages of the tissue.

During the 3d, 4th and 5th days extensive phagocytosis ensued. In fact, all mononuclear cells which now had increased in numbers were heavily phagocytic. Dispersion of the graphite was evidently a function of these cells, for they had a tendency to migrate toward the center of the foreign body, to engulf large quantities of the graphite and then return. With the changes mentioned there was rapid increase and mobilization of fibroblasts. These were spindle-shaped cells with oval nuclei and they were usually nonphagocytic. Fibroblasts are considered only slightly phagocytic and they store engulfed materials rather in the form of fine particles than as large masses, as displayed by clasmatoocytes. Contrary to the apparent dispersal function of the clasmatoocyte the fibroblasts arranged themselves into a wall which largely circumscribed the lesion, walling off the free graphite and graphite laden cells from the peripheral muscle bundles. Thus heavily laden macrophages were massed along the inner surface of the wall of fibroblasts, unable, except in a few places, to penetrate it. But occasional graphite-laden macrophages appeared within the connective tissue capsule; others had migrated to places remote from the lesion.

It was clear, during the earlier days of the mononuclear reactions that the macrophages of the lesion were of two types. During the earlier stages of inflammation, lymphocytes migrated from the capillaries into the area along with the monocytes. These cells were not at once phagocytic; but if one is to judge by size, staining

reactions of nucleus and cytoplasm, it was apparent that here were transitional stages between lymphocytes and typical macrophages. The basophilic rim of cytoplasm around the oval or spherical nucleus increased in extent, the cell engulfed foreign particles and soon was functionally undifferentiated from the other macrophages of the lesion. Such a transformation of the lymphocyte into a phagocytic cell is wholly in accord with the observations of Bloom and Ekola. In studies of the buffy coat of chicken blood,⁹ however, lymphocytes did not transform into clasmatocytes. It is recognized, also, that conclusions drawn from such morphologic evidence alone must be accepted with reserve.

The monocyte, also prevalent in the early reaction, transformed into typical macrophages which became as phagocytic as the tissue clasmatocyte, so that in reactions of 1 week or more it was obviously impossible to detect whether the macrophage was of histogenous or of hematogenous origin. Hetherington has shown that monocytes may increase in size, may lose their typical rosette formation after supravital staining and display a rather patternless distribution of its granules, such as displayed by the clasmatocytes. Thus it appears that these macrophages may have come from three possible sources, namely, the lymphocytes and monocytes of the blood stream and the clasmatocytes of the local connective tissue sheaths of the muscle bundles.

The origin of the fibroblasts which formed the capsule around the foreign body in the muscle is not entirely clear, and yet they are unquestionably of a divergent origin. Fibroblasts are generally considered an end product in that they do not transform into other types of cells, but respond to irritating stimuli by the production of fibrous tissue. There is, however, considerable evidence to the contrary. Von Möllendorff is of the opinion that fibroblasts possess widely divergent possibilities and that they may transform into blood or other tissue cells. Lindsay and Ekola consider the fibroblast a potential clasmatocyte. There is no evidence from our study to indicate that preëxisting fibroblasts may transform into clasmatocytes, although such a relationship is not denied. It appears quite certain, however, that these fibroblasts which produced the fibrous capsule are derived from three sources. Some of them were present in the muscle, and at the time of injection were mobilized around the lesion. Others arose from transformed lymphocytes which were derived from the capillaries, while a third group were transformed clasmatocytes. Furthermore, many of these clasmatocytes, after engulfing quantities of graphite, became a part of the peripheral fibrous capsule and produced characteristic fibrous tissue. Such a transformation of clasmatocytes and polyblasts into fibroblasts has been frequently described.

Comment. Throughout this study the probable origin of the phagocytic cell which characterized the reaction to graphite injected intramuscularly was kept constantly in mind. The endothelial origin of clasmatocytes was first suggested by Mallory and later developed by McJunkin, Foot, Herzog, and Sabin and Doan. Contrary opinions have been expressed by Lang and Clark and Clark. In sections taken from these 10 animals, during the 28 days of observation, we found no evidence to indicate an endothelial origin for the large number of clasmatocytes encountered. Even during the 2d and 3d day, when congestion was marked and diapedesis common, we have never seen an endothelial cell desquamate and migrate through the wall to the lesion.

In another experiment to test the phagocytic activity of the endothelium, we perfused isolated hearts with heparinized whole blood to which a small amount of graphite had been added. After perfusing a heart for 4 to 6 hours, sections of the myocardium, including endothelium, were removed, fixed, stained and examined. Under such conditions graphite granules were never encountered within endothelial cells. True, granules were adherent to the cell membranes, but not actually within the cytoplasm. Smears of the circulating blood, however, showed that the monocytes had engulfed considerable graphite, and they were not unlike those seen in the sections of the intramuscular lesion. The experiment gave no evidence that endothelium was phagocytic, nor that it contributed toward the formation of clasmatocytes.

Definite evidence that clasmatocytes were derived from blood monocytes was presented by Lewis and Lewis. Such changes, however, had been previously suggested by other workers. Our data lead us to conclude that the lymphocytes as well as the monocytes which entered the field of inflammation from the related capillaries transformed into clasmatocytes. Although lymphocytes are not normally phagocytic, yet in the presence of continuous irritation we observed what appeared to be steps in a gradual transition to small but functional clasmatocytes. Likewise the monocytes which normally have a restricted phagocytic tendency and a characteristic granular arrangement, gradually assumed clasmatocytic characters. Thus, after the 4th or 5th day lymphocytic or monocytic clasmatocytes could not be identified from those which were of histogenous origin.

At the conclusion of the period of observation a well defined connective tissue capsule had been formed around the graphite lesion, walling it off from functional muscle. The fibroblasts comprising or forming this wall we believe were of three sources: lymphocytes, local fibroblasts and clasmatocytes. Only a portion of the clasmatocytes apparently transformed into fibroblasts and whether they were of lymphocytic, monocytic or of histogenous origin we do

not know. Clasmatoocytes well laden with dye seemed to become a part of the fibroblastic wall, and apparently gave rise to fibrils, for engulfed graphite particles were detected in the attenuated cytoplasmic bodies.

The ultimate fate of most of the clasmatoocytes appeared to be degeneration. Those that did not transform into fibroblasts were cut off from the circulation, and autolysis quickly ensued.

Conclusions. Clasmatoocytes which were produced on the 2d and 3d day in response to a graphite injection into the sacrospinalis muscle of the rabbit apparently arose from three sources: lymphocytes and monocytes of the blood stream and local wandering cells of the tissue spaces. After the third day these clasmatoocytes could not be distinguished from one another.

The function of the clasmatoocyte was to engulf the foreign material, to disperse and lessen its concentration, to convey portions of it to the blood stream and thence to the reticuloendothelial system.

After the 3d day a fibroblast wall was laid down around the graphite area. This wall restricted the further dispersal activity of the clasmatoocytes and localized the foreign body. Fibroblasts also appeared to arise from three sources: lymphocytes, clasmatoocytes and local fibroblasts. The number of clasmatoocytes, with heavily laden phagocytic materials, which transformed into fibroblasts was small. The larger number, within the circumscribing wall, degenerated.

There was no evidence that endothelium gave rise to clasmatoocytes.

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STUDIES IN RHEUMATIC FEVER.

I. THE NATURAL COURSE OF ACUTE MANIFESTATIONS OF RHEUMATIC FEVER UNINFLUENCED BY "SPECIFIC" THERAPY.

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THE unitary nature of the manifestations of rheumatic fever was first implied when Pitcairn¹ recognized the relationship of pericarditis and rheumatic polyarthrititis. Cheadle² linked the various manifestations which he called the rheumatic series and used the term the rheumatic state to denote the general nature of the disease. Barlow and Warner,³ who described the subcutaneous nodule, suggested the similarity between the changes seen in this lesion and the valvular lesions.

The anatomic basis for the concept of the unitary nature of rheumatic fever was laid with the description^{4,5} of the submiliary myocardial nodule. Studies of the pathologic changes in blood-vessels and supporting tissues^{6,7,8,9} have identified widespread lesions as part of the rheumatic state.

Disturbances in cardiac rate and rhythm¹⁰ and alterations¹¹ in the electrocardiograms have been shown to occur in a large number of patients with acute rheumatic polyarthrititis. Previously acute heart block had been correlated with inflammatory changes in the A-V bundle found at necropsy.^{12,13}

Bacteriologic reports (Poynton and Paine,¹⁴ Small,¹⁵ Birkhaug¹⁶ and Swift¹⁷), claiming a specific or related rôle for organisms found, led to the introduction of antisera and vaccines for the treatment of patients with active rheumatic fever. With the increasing interest in etiologic factors and a better understanding of the nature of the disease the paucity of properly controlled therapeutic studies is surprising.

Lathian¹⁸ recognized the need for clinical control studies. In 1845 he wrote: "Acute rheumatism has experienced strange things at the hands of medical men. No disease has been treated by such various and opposite methods. Venesection has wrought its cure, and so has opium, and so has calomel, and so has colchicum, and so have drastic purgatives. I speak of these remedies in the sense which medical men imply when they talk (as they sometimes do) of this, that, or the other thing being their 'sheet anchor,' meaning that they rest upon it alone for the cure of the rheumatism, and employ other remedies either not at all, or for very subordinate purposes. And, indeed, I bear my testimony to the success of each of these different remedies, so far as that, under the use of each, I have seen patients *get well*."

Gull¹⁹ and Sutton²⁰ studied a series of patients with mint water and observed subsidence of the disease. Hall²¹ (1876), Fagge²² (1881), Reihlen²³ (1886) studied patients treated with salicylates and compared them with cases not receiving the drug. Hanzlik, Scott and Gauchat,²⁴ observing effects on temperature, pulse and symptoms in salicylate treated cases, concluded that the drug possessed no specificity in rheumatic fever.

While there is no question of the therapeutic benefit of antirheumatic drugs, many have undoubtedly felt, as Poynton²⁵ has recently commented, that the rheumatic infection often proceeds unchecked in spite of defervescence and the increased comfort of the patient. He concludes that there are few physicians today who regard salicylates as specific in the treatment of rheumatic fever. Furthermore, Swift²⁶ has stated: "Most statistics indicate that the administration of salicylates does not decrease the incidence of carditis and clinical evidence of this manifestation often appears in patients fully under the influence of antirheumatic drugs." He refers to the figures of Ehrström and Wahlberg,²⁷ in Helsingfors, which indicate that there has been no diminution in the incidence of chronic rheumatic heart disease.

We felt that the study of a control group of patients might be undertaken if we carefully guarded our patients from excessive discomfort by the use of sedatives or hypnotics, whenever necessary. We decided further that we would not jeopardize a single patient by withholding antirheumatic drugs if he appeared extremely ill or in critical danger. To this end we resolved to give antirheumatic drugs to all patients developing rectal temperatures exceeding 105° F. (It was not necessary to do this in a single instance.) All other therapeutic measures, dietary and nursing care, immobilization of joints, applications of cradles, were to be applied with special attention.

We also felt that such a study might be undertaken because of previous experience. The very low mortality from acute rheumatic fever has been realized for a century and prior to the introduction

of the antirheumatic drugs. In our experience when antirheumatic drugs were withheld from patients, for one reason or another, fatalities were most unusual.

Method of Study. Upon admission of the patient the house officer notified one of us, a special detailed history was taken, and the findings of the physical examination were recorded upon a special form. Care was used in determining the exact date of the onset of the disease, and in investigating the patient's antecedent history. Members of the patient's family and his physician were interviewed, and when necessary a home visit was made to amplify such data by a special medical social worker.

Pulse rate and rectal temperature were taken every 4 hours. A complete blood count was done on admission and at least twice a week during the acute stage and once a week until the patient was discharged. An electrocardiogram was taken on admission, and at least twice a week during the acute stage and once a week until the patient was discharged. In cases developing acute pericarditis, or gallop rhythm, or showing first-stage *A-V* block, or any irregularity, electrocardiograms were taken daily or twice daily as indicated. With the subsidence of acute symptoms, tracings were made weekly. Blood cultures were done on all patients at frequent intervals. Skin tests, using streptococcus filtrates, were made at frequent intervals on the patients seen during the 2 years of the study. The results of the bacteriologic studies, skin tests and detailed electrocardiographic studies will be reported elsewhere. As soon as possible after admission a teleoroentgenographic study of the heart was made. Roentgenograms were made of the teeth, nose, throat and accessory sinuses. The urine was examined on admission and frequently thereafter. In addition to being seen by the house officer, patients in the series were seen daily and twice or more daily during the acute stage by us, and notes made on their clinical records. A graphic chart devised by Swift was kept on all cases so that daily correlations could be made. Full-time fellows, special nurses and special medical social service workers were used in addition to the regular hospital staff.*

Treatment. Patients were placed on Gatch beds, painful joints were protected with cotton wool, and if desired camphorated oil was applied. Pressure from bedclothes was relieved by a cradle. Pain was controlled by codein and only once in the course of the study was morphin required. When infected foci were found every effort was made to eradicate them. A special diet was given these patients, and extra efforts were made to force fluids.

During the 2 years 162 patients suffering from acute rheumatic fever were studied. Of this number 50 were treated with salicylates or with vaccine. In this report we are discussing the observations

* From the Rheumatic Fever Fund of the Committee for the Encouragement of Medical Research.

made on 105 patients receiving no form of therapy, which might be believed to be specific, and no antipyretic drug. The patients were divided into three groups: (a) In the first we placed patients with polyarthritis, with acute active manifestations, who had no previous history of rheumatic disease and no heart involvement, and patients who had previously had signs of heart involvement which had been clinically inactive for a long period of time and who showed little or no diminution of cardiac reserve; (b) the second group consisted of patients whose chief manifestation was chorea; (c) the third group consisted of patients with a history of repeated rheumatic infections and advanced structural heart disease. As we were concerned with the natural course of active manifestations of rheumatic fever, we accepted no patients with inactive forms of the disease in this series.

The following criteria* were used to determine the cessation of the active phases of the infection: (1) The rectal temperature was to remain consistently below 99.6° F.; (2) the pulse rate was to remain consistently below 100 per minute; (3) the total leukocyte count was to be below 10,000; (4) absence of cardiac signs such as gallop rhythm, prolonged *P-R* interval, or other significant electrocardiographic changes, and pericardial friction rub; (5) no evidence of pulmonic or pleural infection; (6) no choreiform movements, subcutaneous nodules or skin manifestations of rheumatic fever.† When patients showed no deviation from these standards for a full 2-week period following the last sign of activity, they were considered ready for discharge.‡

Only 47 of the 105 patients remained in the hospital until these criteria had been fulfilled. Fifty-seven patients left for various reasons; 40 because their symptoms had cleared up and they could not be persuaded to remain for the full 2-week period and 17 left despite evidence of activity and against the advice of the physician in charge. All of these patients were much improved.

Forty-seven patients fulfilled all the requirements of this study (35 males, 12 females; see Table 1): These were divided into the 3 groups previously described; 29 in the polyarthritis group, 6 in the chorea group and 12 in the carditis group.

In 15 of the 29 patients in the polyarthritis group sore throat or tonsillitis occurred at the onset of the disease or during the course of the disease. In 2 of the patients with chorea tonsillitis occurred

* The possibility that the criteria in general use as well as those we have used are not adequate must be kept in mind. (Witness the occasional patient presenting unmistakable signs of rheumatic heart disease with an entirely negative history.)

† We are cognizant of the desirability of determining the sedimentation rate of erythrocytes as a sign of continued infection. The study herewith submitted was almost completed when our attention was drawn to the desirability of this procedure.

‡ Only 1 patient of the entire group suffered a second cycle within a month of discharge.

during their hospital stay. Tonsillitis occurred in only 1 of the patients classified as chronic active carditis.

TABLE 1.—MANIFESTATIONS OF RHEUMATIC FEVER.

Patient.	Age.	Sex.	No. of present attack.	Duration of disease (onset to discharge).	Duration of signs or symptoms.	Days in hospital.	Fever.	Tachycardia.	Sore throat or tonsillitis.	Polyarthritis.	Pericarditis.	A-V block.	Galloperhythm.	Heart failure.	Pleurisy.	Pneumonitis.	Skin manifestations.	Subcutaneous nodules.	Chorea.	Died.
Polyarthritis.																				
1. W. S.	15	M	1	23	7	22	+	+	..	+										
2. J. K.	39	M	4	25	11	22	+	+	..	+										
3. L. R.	12	F	3	26	11	24	+	+	+	+		+								
4. H. G.	18	M	1	37	20	26	+	+	+	+										
5. S. K.	31	M	2	58	30	46	+	+	..	+										
6. E. W.	18	M	2	49	32	43	+	+	..	+					+					
7. M. W.	23	M	1	65	42	56	+	+	+	+										
8. M. D.	47	M	3	60	45	58	+	+	..	+		+								
9. F. N.	46	M	2	60	46	57	+	+	..	+										
10. E. B.	44	M	4	69	49	46	+	+	..	+		+								
11. C. V.	24	M	1	81	50	55	+	+	..	+										
12. A. Ll.	33	M	1	93	54	88	+	+	..	+										
13. A. Le.	13	F	2	73	56	60	+	+	..	+		+	+							
14. J. D.	36	M	2	71	57	50	+	+	..	+										
15. H. K.	21	M	1	80	57	75	+	+	+	+		+			+					
16. W. M.	30	M	4	83	60	83	+	+	..	+										
17. L. L.	38	M	4	75	61	70	+	+	..	+										
18. S. Ma.	22	M	1	92	70	71	+	+	..	+										
19. D. I.	27	M	2	90	72	52	+	+	..	+										
20. S. Mi.	35	M	1	95	72	79	+	+	+	+					+					
21. M. P.	15	F	2	88	73	85	+	+	..	+		+						
22. O. McG.	38	M	4	95	73	92	+	+	..	+		+	+	+	..		+			
23. A. S.	45	M	2	88	74	79	+	+	..	+		+	+	+						
24. H. S.	31	M	1	95	77	79	+	+	..	+		+	+					
25. G. deM.	17	M	1	98	78	78	+	+	+	+						+				
26. G. H.	31	M	2	108	82	105	+	+	+	+		+	+	+	+					
27. H. M.	24	M	2	101	87	95	+	+	..	+		+	+	+						
28. W. I.	25	M	1	113	87	92	+	+	+	+		+						
					not less than 25															
29. C. O. Chorea.	24	M	3	..	25	53	+	+	..	+										
30. B. D.	14	F	1	70	56	40	+	+	+	
31. H. W.	13	M	1	71	56	55	+	+	+	
32. J. M.	15	M	1	112	87	105	+	+	+	
33. A. P.	12	F	2	112	92	58	+	+	+	+		+	
34. R. B.	12	M	1	176	113	148	+	+	+	
35. A. C.	12	F	1	167	152	77	+	+	+	+		+	
Active chronic carditis.																				
36. E. G.	14	F	4	15	+	+		+	+	..	+	+
37. C. B.	33	F	5	20	+	+	+	+	+
38. E. C.	13	M	1	34	+	+	+	+	+
39. J. S.	13	M	5	36	+	+	+	+	+
40. E. P.	29	M	2	36	+	+	+	+	+
41. P. H.	30	F	3	38	+	+	+	+	+
42. M. P.	25	F	?	84	+	+	..	+		+	+	+
43. J. U.	18	M	3	94	+	+	+	+	+
44. I. H.	15	F	?	129	+	+	+	+	+
45. S. I.	34	M	4	140	+	+	+	+	+
46. W. O'B.	31	M	5	148	+	+	+	+	+
47. M. D.	25	F	1	169	+	+	+	+		+	+	+

TABLE 2.—AGE DISTRIBUTION.

[illegible]

Pericarditis occurred in 5 patients in the polyarthritis group and in 1 patient in the chronic active cardiac group. Murmurs alone were considered too indefinite a sign of activity to be used as evidence of carditis.

Gallop rhythm occurred in 4 patients of the polyarthritis group. Signs of congestive heart failure appeared in 9 of the polyarthritis group and in all of the chronic active carditis group.

Pleurisy developed in 2 patients in the polyarthritis group and in 4 patients in the chronic active carditis group.

Pneumonitis of a type not characteristic of lobar pneumonia was seen in 3 patients, 1 in the polyarthritis and 2 in the chronic active carditis group. These were believed to be rheumatic pulmonary manifestations.

Skin manifestations occurred in 6 patients, 1 of these was in the polyarthritis group and 5 of the chronic active carditis group, and 1 patient in the polyarthritis group developed subcutaneous nodules. In considering the manifestations in relation to the possible effects of therapeutic procedures, it is to be emphasized that there is great variability as to the type and number.

TABLE 3.—FREQUENCY OF MULTIPLE MANIFESTATIONS IN RELATION TO THE DURATION OF SIGNS OF ACTIVE RHEUMATIC FEVER.

	Duration of signs or symptoms.		
	46 days or less.	47 to 70 days.	70 to 87 days.
Number of cases	9	9	10
Fever	9	9	10
Tachycardia	8	6	10
Sore throat	3	4	8
Polyarthritis	9	9	10
Pericarditis	0	1	4
A-V block	2	4	3
Gallop rhythm	0	1	3
Heart failure	0	1	8
Pleurisy	1	0	2
Pneumonitis	0	0	1
Skin manifestations	0	0	1
Subcutaneous nodules	1	0	0
Chorea	0	0	0

A relation was noted between the duration of active signs or symptoms and the number of manifestations. With activity for less than 46 days (9 patients), fever, tachycardia and polyarthritis were accompanied by tonsillitis (or sore throat) in 3 cases, by A-V block once, by pleuritis once and 1 appearance of subcutaneous nodules (Table 3). With activity from 46 to 70 days (9 patients), fever, tachycardia and polyarthritis were accompanied by tonsillitis (or sore throat) in 4 cases, by pericarditis once, A-V block 4 times, gallop rhythm once (during A-V block), signs of heart failure once. With signs of disease for more than 70 days (and in our observations up to 87 days), the frequency of multiple manifestations is seen to be sharply increased. In this group all 10

patients had fever, tachycardia and polyarthrititis. Tonsillitis (or sore throat) occurred 8 times, pericarditis 4 times, *A-V* block 3 times, gallop rhythm 3 times (twice in association with *A-V* block). Signs of heart failure appeared in 8 patients, pleurisy occurred in 2, pneumonitis in 1 and a skin manifestation in 1.

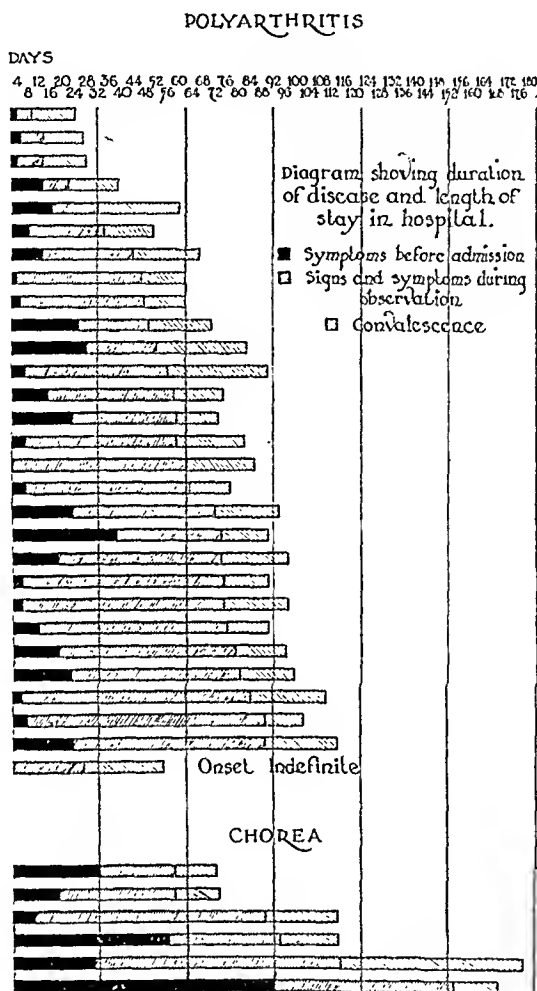


CHART I.—A diagram showing the duration of disease and the length of stay in the hospital of 29 patients with polyarthrititis and 6 patients with chorea.

Swift²⁸ reported 72 cases "treated according to the accepted methods, with rheumatic drugs for arthritis and high fever, removal of such disease foci as tonsils or teeth and treatment of diseased sinuses or other suspected foci." He used criteria identical with those used by us in considering patients ready for discharge. If we exclude 24 of his cases which were below the age of 14 years we have a group of 48, comparable to this series both in number and age grouping. In his total group the illness varied between 30 and 220 days. Although the two groups are not absolutely comparable,

we think it is evident that the elimination of antirheumatic drugs, at least, did not prolong the duration of the disease (Chart I).

Patients with a history of previous rheumatic infections, showing badly damaged hearts, and who had as a presenting symptom signs of subacute cardiac activity, had the longest period of illness. In this group the only deaths occurred. Patients with chorea had the next longest period of active symptoms, and patients admitted with polyarthritis as the presenting symptom had the shortest duration of the disease.

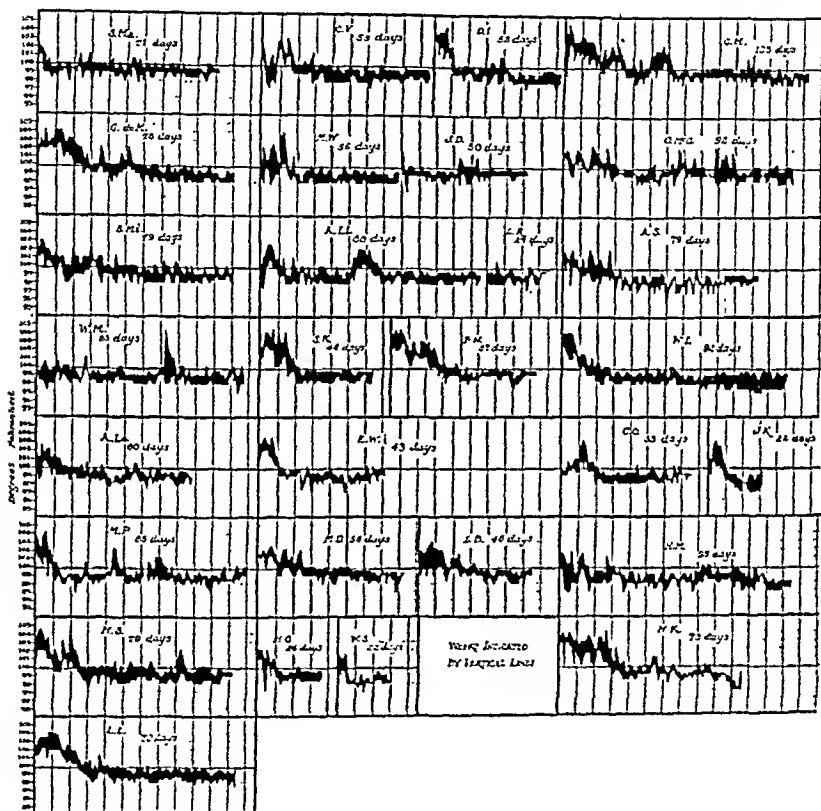


CHART II.—Temperature variations in 29 patients with rheumatic fever and polyarthritis.

Duration of Illness. The illness was considered to have begun upon the first definite history of rheumatic manifestation and to continue until the patient was free from any evidence of activity for 2 weeks. In the group of patients with chronic carditis the onset was more indefinite than in the other 2 groups. We believe that the period of activity often extends for years.

No relationship was found between the length of the attack,

length of illness, sex, age and number of attacks. It was also found that there was no appreciable difference in the duration of the attack when this was correlated with the time of the entrance to the hospital, whether early or late in the disease. The longest period of activity was observed in patients with chorea or chronic active carditis.

In the polyarthrititis group activity was increased in patients who developed pericarditis or signs of heart failure and slightly increased for those who developed a *P-R* interval of the electrocardiogram

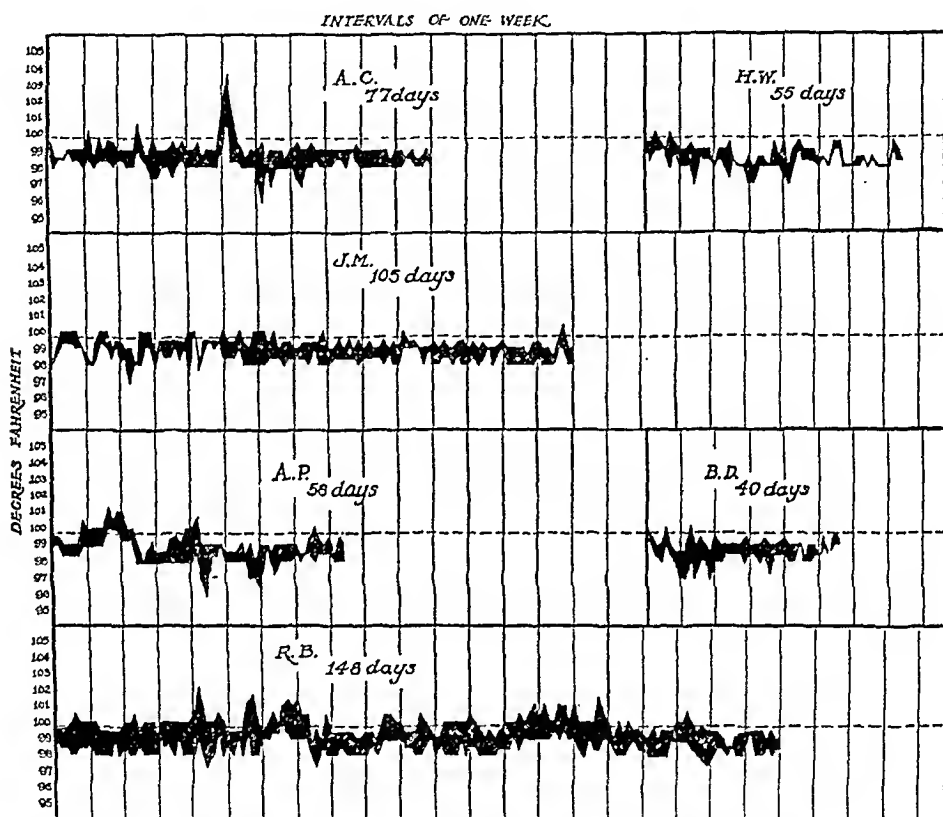


CHART III.—Temperature variations in 6 patients with rheumatic fever and chorea.

of over 0.2 second. However, none of the patients with pericarditis or prolonged interval had such manifestations alone. When either of these manifestations occurred the activity lasted for 6 weeks or more. There were 2 exceptions, 1 patient in the polyarthrititis group and 1 patient in the chronic active carditis group who had a rapidly fatal course.

Tonsillitis, at the onset or during the disease, was present in 9 of the patients (Nos. 20 to 28, inclusive) in the polyarthrititis group, whose illness was longest and characterized by multiple manifestations and considered the most severely ill.

Temperature. In the polyarthritides group 10 patients had a single bout of fever, 6 patients had 2 cycles, 3 patients had 3 and 1 patient had 4 cycles of fever. The shortest duration of any cycle of fever was 5 days, the longest 56 days. The highest temperature in our group was 105° F. Thirteen of the patients had temperatures which ranged up to 104° F. As a rule, in the polycyclic forms the second cycle was not as high and the duration of fever was not as long, but this did not always hold true. As might be expected, the duration of the fever was usually associated with new manifestations or recurrences of old manifestations of rheumatic fever (Chart II).

In general, it may be said that the temperature of the patients studied tended to subside spontaneously. It is possible to control fever in rheumatic fever by salicylates or other antirheumatic drugs, but it is recognized that such drugs must be withdrawn during con-

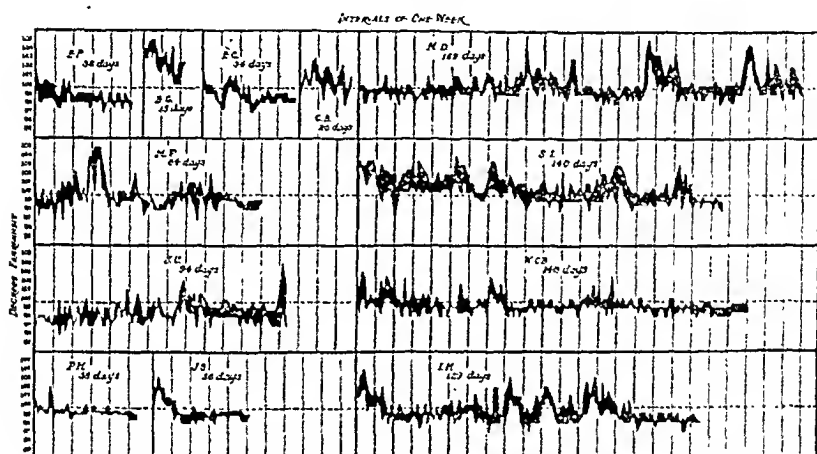


CHART IV.—Temperature variations in 12 patients with rheumatic fever and chronic active carditis.

valescence in order to determine that the active process of the disease has ceased, and that unless patients are subjected to a period of observation, free from the administration of antirheumatic drugs, many patients will be discharged while the disease is still active.

Our experience shows us that the temperature of rheumatic fever patients becomes and remains normal without the use of antirheumatic drugs. Further, more than half of the patients had only a single cycle of fever. It is important to emphasize these spontaneous remissions in considering any mode of treatment. In the chorea group all of the patients did not have fever, but those who did ran a low-grade and persistent elevation of temperature. Fever in the patients in the chronic active carditis group, as a rule, persisted longer and was irregular, though in some it may have been said to be polycyclic (Charts III and IV).

Joint Involvement. Considering all joint symptoms together without reference to intensity, 2 cases were found to have a maximum of 16 joints involved, 1 case had only 2 joints involved, while 16 of the 30 showed involvement of 6 to 12 joints.

With reference to the intensity of joint involvement, we find that 24 cases had severe arthritis, 1 of these had 12 joints acutely inflamed and extremely painful at one time; but of the 24 cases 12 had 6 joints or less involved; 2 cases had only 1 joint severely inflamed (Chart V).

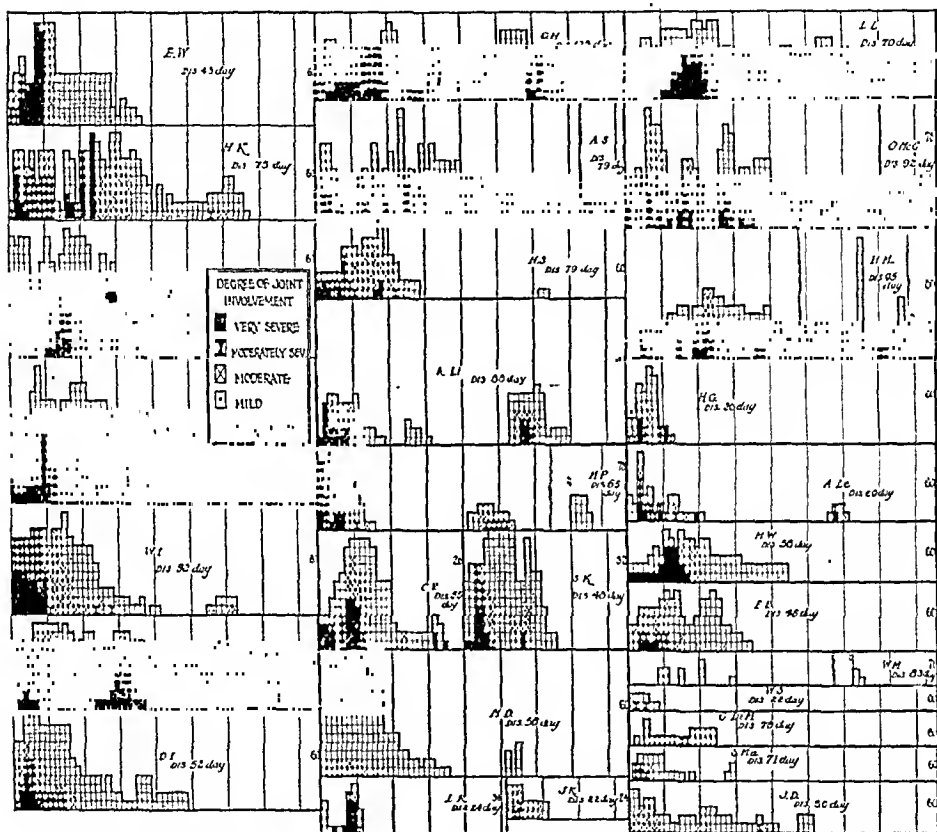


CHART V.—A chart to show the degree and duration of joint involvement in 29 patients with rheumatic fever and polyarthritis.

Recurring attacks were always milder than the initial attack. In only 1 of the recurrences was polyarthritis observed which could be rated as severe.

Untreated arthritis usually subsided in a week (22 out of 29). In over half of the patients there was no recurrence of arthritis, and when there were recurrences they uniformly affected fewer joints and were less severe and of shorter duration than the initial attack. Cases were encountered which showed spontaneous subsidence of arthritis as abrupt and complete as those seen in cases in which salicylate therapy has been instituted.

Heart Block. Of 29 cases of polyarthrititis 9 developed *A-V* block, using the *P-R* interval of 0.2 second as a criterion for the presence of block. It is realized that this is a strict interpretation of auriculo-ventricular block, but all of these patients satisfied the criterion laid down by Cohn and Swift, that there be an increase of 0.06 second above the normal. Of 12 cases of chronic carditis 4 devel-

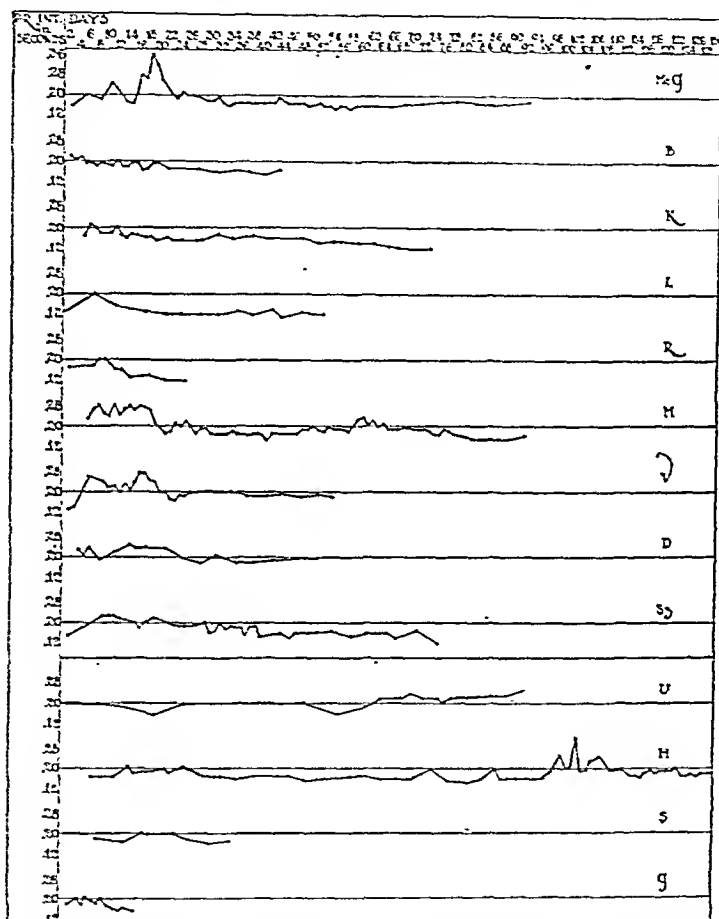


CHART VI.—A chart to show variation in the *A-V* conduction time during the course of rheumatic fever uninfluenced by salicylate therapy. Time in days is plotted along the abscissa; the *P-R* interval in seconds is plotted along the ordinate. The first 9 curves are from patients with rheumatic fever and polyarthrititis; the last 4 curves are from patients with rheumatic fever and chronic active carditis.

oped *A-V* block. It would seem from these cases in both groups, as well as from a much wider experience with patients receiving salicylates, that *A-V* block, occurring in the course of acute cardiac manifestations of rheumatic fever, is subject to wide variations and is usually of short duration. Its occurrence may be monocyclic or polycyclic, and its persistence may be variable (Chart VI).

The maximum $P-R$ interval in this group of cases was 0.36 second. It usually ranged between 0.2 and 0.26 second. The variations in block as to degree, persistence and recurrence are important when one attempts to determine criteria for judging the effect of a therapeutic agent on $A-V$ block. The consideration of the presented facts showed that in the course of acute rheumatic fever unmodified by therapy there are wide and inconstant variations of the $P-R$ interval. Elsewhere a study²⁹ has been reported from this clinic in which it has been shown that variations of the $P-R$ interval are not influenced by salicylate therapy.

Tachycardia. In the polyarthritis group 15 patients had a single cycle of tachycardia. Five had 2 and 4 had 3 cycles of tachycardia. In 4 patients no tachycardia was observed during the hospital stay. The shortest period of tachycardia was 24 hours and the longest continuous period was 52 days. The highest rate noted was 140 and occurred in 1 patient. The maximum rate in 8 patients was 130 beats per minute; in 10 it was 120; in 5 it was 110; in 2 it was 100; in 3, 95. Tachycardia as a sign of activity occurred alone sometime during observation in 8 patients of the polyarthritis group. Frequent isolated days of tachycardia were noted but, as a rule, elevations of the pulse rate above 100 beats per minute were associated with other manifestations. We encountered 4 instances where the pulse rate never exceeded 95, and ranged between 85 and 95 in spite of the presence of fever, inflamed joints, or $A-V$ block. In 5 patients tachycardia, persisting after the subsidence of all other manifestations, prolonged the illness from 1 to 18 days.

In the chorea group tachycardia was present on admission in only 1 patient. The maximum rate was 130, noted in 1 patient; 4 exhibited a maximum rate of 110, and the 6th patient had a maximum rate of 120. One of the 6 patients exhibited tachycardia with no other manifestation during the hospital stay for a period of 2 weeks. In the other instances tachycardia was associated with other active manifestations and occurred as an isolated observation rarely in 2 cases. In this group sustained tachycardia was unusual. Where it did occur it was associated with other intercurrent manifestations, that is, tonsillitis or sore throat.

In the group of chronic active carditis tachycardia accompanied fever in 5 patients. It lasted less than 1 week in 1 case and occurred alone in 4 cases. It was altogether absent in 1 instance.

In general, it may be said that tachycardia like fever tended to subside spontaneously. Tachycardia in the absence of fever or any other manifestation is not an unusual sign in the natural course of active manifestations of rheumatic fever.

Fatalities. Deaths occurred only in the chronic active carditis group. There were 6 deaths in patients who were admitted with advanced structural heart disease and signs of active rheumatic fever. Progressive heart failure consequent and in association with active infection accounted for 5 of these deaths. The sixth was in

a young girl who ran a rapidly downhill course characterized by fever, pericarditis, *A-V* block, profound toxemia and moderate congestive failure.

Summary. In adolescence and adult life the acute manifestations of rheumatic fever tend to subside spontaneously. These manifestations vary in number, degree and duration.

If changes in the number, degree and duration of manifestations are used as criteria for determining the effect of therapeutic agents such changes must be compared either with a standard control group of rheumatic fever patients of known age, sex, racial and proper geographic distribution, of sufficient size to meet statistical requirements; or controlled cases must be studied simultaneously with cases receiving "specific" therapy, in sufficient number so that it may be determined whether or not the effects associated with treatment are not simply variations attendant on the natural course of the disease.

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FUNCTIONAL BUNDLE-BRANCH BLOCK (PARTIAL) PARADOXICALLY RELIEVED BY VAGAL STIMULATION.

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ALTHOUGH bundle-branch block is in the vast majority of cases caused by anatomic changes affecting one of the bundle branches, it was demonstrated by Cohn and Lewis¹ and other observers that it may occur without any demonstrable lesion. To explain such phenomena, we must assume the presence of certain functional disturbances interfering with the free passage of the impulse along one of the branches.

The possible factors that may cause such disturbances during life without leaving any permanent damage discoverable on post-mortem examination are bundle-branch fatigue, toxic states, local interference with the blood supply, and nervous inhibition. In all these cases, variability in the grade and form of block from time to time, corresponding with the variations in the degree of the causative factor or factors, is to be expected.

There are no clear-cut clinical examples found in the literature of bundle-branch block caused by toxic states. Experimental evidence of such conditions, however, is found in the work of Lewis and Mathison.² Likewise, no clinical example of such block as being caused by local diminution of the blood supply to one bundle branch has been recorded. Oppenheimer and Williams³ report a case of complete heart block with frequent shifting and changing electrocardiographic complexes during life, and the only post-mortem lesion was sclerosis of the nodal artery. We may, therefore, infer from this case that a similar condition may also account for occasional bundle-branch block.

Although toxic states and local interference with the blood supply as causes of bundle-branch block have not fully been established, fatigue of the conducting apparatus in the ventricles as well as vagal inhibition causing such block are fairly well proved. It is true that the clinical reports even of such instances are not many.

Noteworthy examples of fatigue as the cause of such block and other aberrations of ventricular complexes are those of Samet,⁴ Stenström⁵ and Willius and Keith.⁶ Samet's case was a male, aged 50 years, presenting evidence of arteriosclerotic heart disease with periods of 2 to 1 heart block. The *Q-R-S* conduction time was normal during the period of block, but greatly prolonged when the ventricles responded to every auricular impulse. In other words, prolonged rest of the bundle branches caused by auriculoventricular block

restored them to normal functional ability. Stenström presents 2 cases of bundle-branch block. In each, the block was abolished by slowing the heart. Willius and Keith present 3 cases with aberrant *Q-R-S* complexes during decompensation, which returned to normal when compensation was restored. They attribute such aberrances

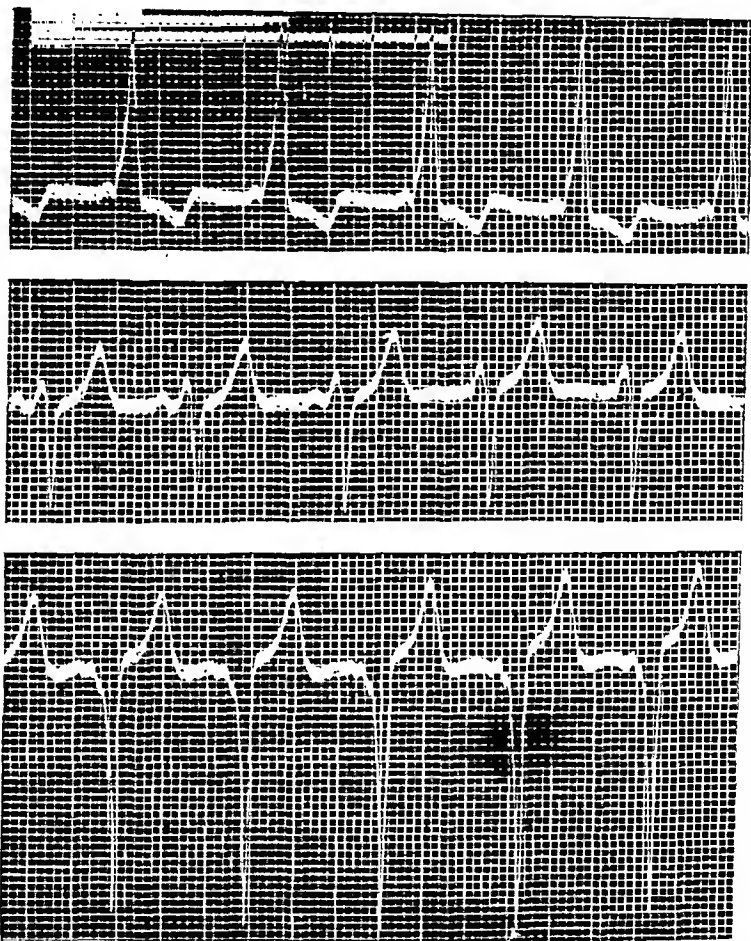


FIG. 1.—Right (new terminology, left) bundle-branch block. Rate about 84, rhythm regular. The *P-R* interval is very short, the maximum being 0.10 second. There is a definite variation in the lengths of the *P-R* interval even in the same lead the shortest being 0.04 second. The *Q-R-S* conduction time is 0.12 to 0.14 second.

to fatigue of the interventricular conducting apparatus during decompensation.

The more common cause of functional bundle-branch block is nervous inhibition, the vagus being the effective nerve.

That the vagus influences the interventricular as well as the supraventricular portions of the conducting apparatus was demonstrated

by Ritchie,⁷ Cohn,⁸ and Einthoven and Wernuge.⁹ Wilson was able to produce bundle-branch block by vagal stimulation in a very interesting case that he reported.¹⁰ In a recent paper by Wolff, White, and Parkinson,¹¹ 11 cases of bundle-branch block occurring in young and otherwise healthy people are described. In each case, the block was abolished by exercise or atropin which removed vagal effect, demonstrating the dependence of such block on the vagus. We have recently seen a similar case in the cardiac clinic of the New York Post Graduate Hospital. A 16-year-old boy came for examination because he was told that he had heart disease. He had

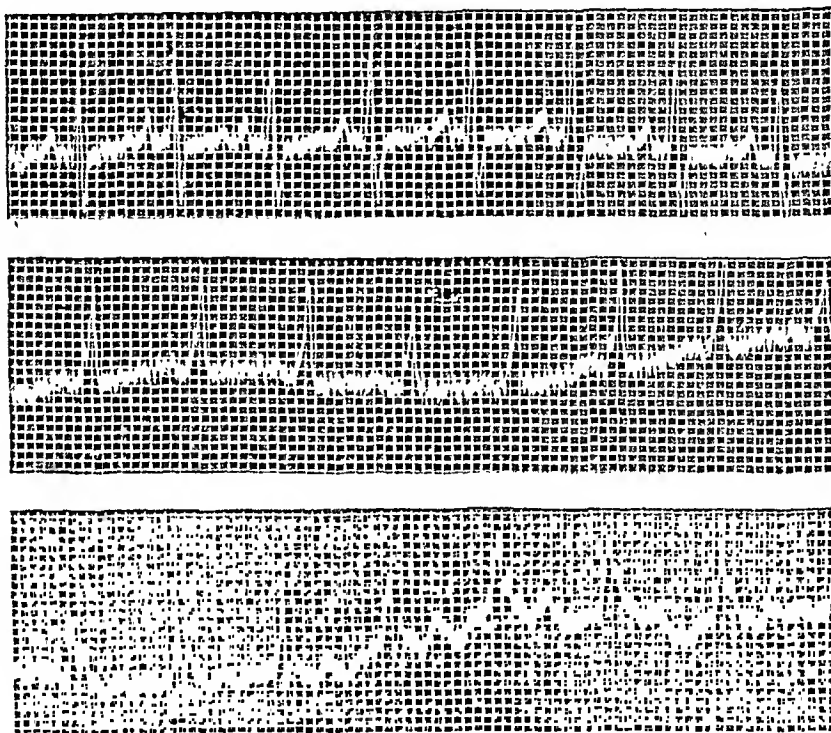


FIG. 2.—Tracings obtained from the same patient as in Fig. 1 after 30 hops on one leg. Rate 150; regular sinus rhythm. *P-R* conduction about 0.16 second. *Q-R-S* conduction 0.08 second.

no complaints, and the physical examination revealed nothing abnormal except a faint transient systolic murmur. The electrocardiogram (Fig. 1), however, showed bundle-branch block with a short *P-R* interval as described by the above authors. After exercising the patient, the ventricular complexes assumed a more normal appearance. The *Q-R-S* conduction time became normal and *P-R* interval was prolonged (Fig. 2).

All these instances prove conclusively the possibility of the occurrence of bundle-branch block as a result of excessive vagal activity in certain cases. It would therefore appear irrational and paradoxical to expect the removal of such block by vagal stimulation.

The following case showing such a condition is therefore considered interesting enough to be put on record.

Case Report. C. E., male, aged 41 years, real estate operator, married, complained of pain in the precordium. The pain appeared spontaneously about once in 3 days, each attack lasting only about 2 or 3 seconds, and was described as sudden, sharp, and knifelike in character. Between these attacks, the patient felt quite comfortable, never experiencing any dyspnea, palpitation, precordial oppression, or any other symptoms attributable to heart disease. He was able to carry on his work well, doing at times a great deal of climbing hills without the slightest discomfort.

His father died at 44 years of age as a result of an accident, and his mother died at 52 of pneumonia. One brother was living and well.

His personal habits were good except for indulgence in alcohol and tobacco. He was married 7 years and had had 1 child who is living and well.

His past morbid history consisted of measles and whooping cough in childhood, appendectomy at 20 years, and gonorrhea at 22 years with no sequelæ.

The physical examination revealed a well-developed, healthy-looking male, calm in demeanor. Pupils reacted normally. No exophthalmos, no nasal or evident accessory sinus pathology. Teeth and gums were normal. Tonsils were hypertrophied and chronically diseased. Neck was negative. Chest was of normal shape, no asymmetry, bulging or abnormal pulsations. Lungs were negative.

The heart and aorta were of normal size and shape, as evidenced by physical and fluoroscopic examinations. The maximum apex impulse was in the fifth interspace, about 9 cm. from the midsternal line, and percussion dullness extended about $\frac{1}{2}$ cm. further to the left in the same interspace. The right border in fourth space was about 4 cm. from the midsternal line. The transverse arch measured about $5\frac{1}{2}$ cm. The heart rate varied from 65 to 75 beats per minute. There was a slight degree of sinus arrhythmia and an occasional premature contraction. The first sound at the apex was long, dull, and somewhat reduplicated, and the second sound was weak, the pulmonic being greater than the aortic. There were no murmurs. The peripheral arteries were somewhat thickened, and the pulse was of medium quality with an occasional intermission. The blood pressure was systolic 120, and diastolic 65.

The abdomen and extremities were negative.

The Electrocardiogram. Fig. 3 shows portions of the electrocardiogram obtained by the standard leads, on a standardization of 10 mm. being equivalent to 1 millivolt. The impulse is seen to originate in the normal sinus area at a rate of about 65 per minute. The *P-R* conduction is normal. The *Q-R-S* complexes show the following features: they are of low voltage, the maximum being 0.45 mv.; the conduction time is prolonged upward of 0.12 second, and they are markedly slurred and notched. The *P* and *T* waves assume a normal directional course except in the third lead, where the *T* wave is diphasic.

The moderate sinus bradycardia and slight arrhythmia suggested the possibility that vagal influence was the underlying cause of the interventricular conduction disturbance. I have attempted, therefore, the removal of such influence by exercise. Fig. 4 is a part of the tracing in the second lead obtained after the patient was made to hop on one leg about 30 times in 1 minute. It will be noted that the only change is an increase heart rate at the expense of a shortened diastolic period. The *Q-R-S* complexes retain the same abnormal features as before exercise, except that their voltage is somewhat increased. One premature ventricular contraction is seen not followed by any compensatory pause, and the succeeding complexes were of the same abnormal type as before.

After a rest period sufficient to return the rate to the previous level, an attempt was made to see what effect vagal stimulation would have on the abnormal $Q-R-S$ complexes. Carotid sinus pressure was employed for that purpose. Fig. 5 is a tracing in the second lead obtained on right vagal

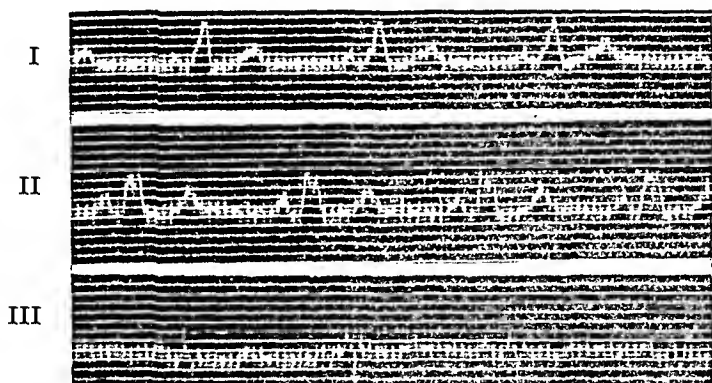


FIG. 3.—Rate about 55, slight sinus arrhythmia. $P-R$ interval normal. There is an increase in the $Q-R-S$ conduction time to 0.12 second with marked slurring and notching, and low voltage, the maximum being 0.45 millivolts. The $T-R$ interval is 0.44 to 0.53 seconds.

stimulation. A slowing of the heart to about 60 per minute for about two cycles is seen, followed by a ventricular premature contraction with a compensatory pause of about 0.8 second. The next $Q-R-S$ complex appears perfectly normal, the conduction time being 0.06 second. This is again followed by a series of the usual abnormal $Q-R-S$ complexes on continuing the right vagal stimulation.

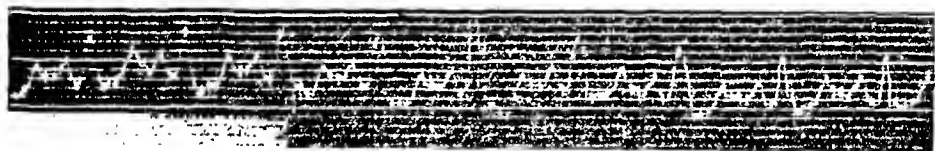


FIG. 4.—Obtained after exercise. The $Q-R-S$ conduction time remains at 0.12 second, with slurring and notching. One ventricular premature contraction is seen, not followed by any compensatory pause, and with no change in the character of the subsequent complexes.

Left vagal stimulation, on the other hand, yielded different results. Fig. 6 is a tracing in the second lead obtained by such stimulation. Four of the usual abnormal complexes are seen with a gradual increase in the $T-R$ interval. This is followed by a series of normal ventricular complexes, at a rate of about 55 per minute, with marked sinus arrhythmia. The $Q-R-S$ conduction time is about 0.06 second, with no notching or slurring, and about 1 mv. This persisted as long as left vagal pressure was maintained. The T waves are the same with the abnormal as with the normal $Q-R-S$ complexes.

Discussion. The electrocardiogram presented in this case, unmodified, corresponds to the so-called "arborization block" of Oppenheimer and Rothchild.¹² The $Q-R-S$ complexes are prolonged beyond 0.1 second, notched, are of low voltage and there is the absence of the



FIG. 5.—Second lead of tracing obtained on right vagal pressure: The $T-R$ interval does not exceed 0.56 second in any cycle. The $Q-R-S$ complexes show the same abnormalities as in Fig. 3, Lead II. One ventricular premature complex is seen, followed by a compensatory pause of 0.8 second, and this is followed by a normal $Q-R-S$ complex.



FIG. 6.—Tracing obtained on left vagal pressure: The first four $Q-R-S$ complexes are of the abnormal type, with $T-R$ intervals of 0.64, 0.72, 0.76, and 0.72 seconds respectively. Following the fourth complex, there is a series of normal complexes persisting as long as vagal stimulation was done. The $T-R$ intervals are 0.68, 0.72, and 0.88 seconds respectively. Only part of tracing is shown.

typical character of the *T* wave found in complete bundle-branch block, which is opposite in direction to the major deflection.

We need not discuss here the correctness of or objections to the term "arborization block," which has been done amply by such authorities as Wilson and Hermann¹³ and Lewis.¹⁴ Suffice it to say that the ease with which the normal complexes were restored in this case would tend to prove the contention of the latter authors that the *Q-R-S* conduction disturbances in such cases are dependent upon a delay in one of the main branches of the bundle rather than in the arborizations and muscle mass. Depending upon the amount of delay, there is a corresponding variation in the algebraic summation of the dextro- and levocardiogram resulting in the abnormality.

That normal complexes were so easily restored by the vagal reflex is also sufficient proof that the condition was not dependent in this case upon any anatomic pathology. The interesting question then is "what caused this conduction disturbance, and how did vagal stimulation relieve it?" Although we must employ theoretical conceptions to answer it, we have sufficient evidence in the electrocardiogram to prove that either vagal inhibition or fatigue is responsible for the condition—most likely the latter.

That vagal inhibition may effect the bundle branches was shown in the preliminary discussion of this paper, and the conception of its partial interference with the passage of the impulse along the right bundle branch, is plausible. Left vagal stimulation which would theoretically increase inhibition along the left branch might thus have a tendency of producing normal *Q-R-S* complexes, as the impulse would reach the muscle masses of both ventricles simultaneously, even if more slowly. There are, however, two objections to this theory. (1) Adequate proof has not yet been brought forward to show the direct effect of each vagus nerve upon the corresponding bundle branch. (2) Assuming that the normal ventricular complex produced in this case by left vagal inhibition was a direct effect of that nerve upon the left bundle branch, we should expect some auriculoventricular block at the same time. This can be easily understood when we realize that regardless of where the retardation of the impulse coming from the auricles to the ventricles takes place—whether in the supraventricular area or lower down—the end result should be the same. In this case, however, there was no prolongation of the *P-R* interval during the period when normal ventricular complexes were produced. This fact alone is sufficient to discard this theory.

The second theory, namely that of fatigue of one of the branches causing the disturbance, finds more support. It also explains the relief obtained by left vagal stimulation.

If we represent the period of electrical inactivity of the conducting apparatus of the ventricles by the *T-R* interval, starting at the end of the *T* wave and ending at the inception of the *R* wave, and if we

study carefully this interval from cycle to cycle, we find that when its duration is less than 0.64 second, it is followed by an abnormal $Q-R-S$ complex. Thus, the minimum $T-R$ interval in Fig. 3 is 0.44 second and the maximum 0.52 second, and the $Q-R-S$ complexes are all abnormal. In Fig. 4, these intervals are greatly shortened and the respective $Q-R-S$ complexes remain definitely aberrant, even with the marked increase in the heart rate. Examining Fig. 5, which is the tracing obtained by right vagal pressure, we find that none of the $T-R$ intervals reaches 0.64 second. One notable exception in this tracing is a ventricular premature contraction, followed by a long compensatory pause of 0.8 second, and the succeeding $Q-R-S$ complex is normal. This in itself proves that giving the ventricular conducting apparatus more time to rest, the $Q-R-S$ complex following such rest is normal. It is also noteworthy to find that a similar premature contraction in Fig. 4, not being associated with a compensatory pause, is not followed by a normal complex. The best proof of this contention is found in Fig. 6 obtained by left vagal stimulation. The $T-R$ interval in the first three cycles associated with abnormal $Q-R-S$ complexes are 0.4, 0.5, and 0.5 of a second respectively. Following these, and caused by vagal stimulation, there is a definite slowing of the heart to about 55 beats per minute and the $T-R$ intervals are 0.64, 0.72, 0.76, 0.72, 0.68, 0.72, and 0.88 of a second respectively, each of which is followed by a normal $Q-R-S$ complex. In other words, longer rest restored normal functional activity. This clearly indicates that fatigue is the underlying cause of the disturbance. Judging from these figures, we find that as short an interval as 0.08 second more than the maximum $T-R$ interval of 0.56 second, which is not followed by a normal complex, is sufficient to restore normal rest to the interventricular conducting apparatus in this case.

We may conclude, then, that it was not the direct vagal effect on the bundle branches which produced the results in this case. It was merely the slowing of the impulse formation in the sinoauricular node, under left vagal stimulation, giving increased rest to the conducting apparatus of the ventricles, and it was this increased rest which restored normal conduction in this case.

Summary. 1. Bundle-branch block, complete and partial, may be functional in origin, caused predominantly by vagal inhibition and fatigue.

2. Restoration of normal $Q-R-S$ complexes in such cases may be accomplished by removal of vagus inhibition where vagal effect is the underlying cause, and by local rest where fatigue is the cause.

3. A paradoxical case is reported where left vagal stimulation apparently removed rather than caused such block.

4. The underlying functional disturbance in this case was apparently fatigue of one of the bundle branches which was sufficiently relieved by increased vagal slowing to permit normal bundle-branch conduction.

5. Abnormal Q-R-S complexes occurred after as long a rest as 0.56 of a second, and normal complexes were restored by additional rest of 0.08 of a second.

NOTE.—I am indebted to Miss Marcella F. Hughes of the Electrocardiographic Laboratory of the New York Post Graduate Hospital for the preparation of the electrocardiograms in Figs. 1 and 2 for publication.

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WHAT HAPPENS EVENTUALLY TO PATIENTS WITH HYPERTHYROIDISM AND SIGNIFICANT HEART DISEASE FOLLOWING SUBTOTAL THYROIDECTOMY?*

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TREMENDOUS strides have been made in recent years in the care of patients suffering from hyperthyroidism, particularly in those cases with gross evidence of cardiac involvement. As a result of the intro-

* This study was in part conducted under a grant from the Proctor Fund for the Study of Chronic Disease.

duction of basal metabolism determinations into clinical work, the refinements in surgical technique, the use of iodine in pre-operative treatment and especially the clinical recognition of previously undetected types of hyperthyroidism, many patients now respond most satisfactorily to treatment who, in the past, either would have succumbed to operation or would not have been recognized as suffering from thyroid disease. As Lahey well expressed it, there is now practically no "thyrocardiac" who cannot be treated surgically with a high degree of safety and hopefulness.¹ Much has been written about clinical recognition of these "masked" cases,^{2,3,4,5,6,7,8} demonstrating that the immediate effects of proper treatment are most extraordinary. Many patients with moderate or advanced heart failure or angina pectoris who have been refractory to all the ordinary therapeutic procedures have regained compensation and have been restored to normal or fairly normal activities following a subtotal thyroidectomy. It is the purpose of this study to see what the ultimate condition of these patients may be, and to ascertain whether the marked improvement is temporary or permanent. It is further hoped to distinguish the rôle played by the thyroid gland in the production of the cardiac symptoms from that due to other independent concomitant factors. In other words, we were desirous of studying the status of as many of these "thyrocardiacs" as possible years after operation. Particular attention was directed to the changes in the blood pressure, size of the heart, murmurs and irregularities of the heart. Finally, we were interested to learn if the improvement was permanent, and, in general, what the subsequent health of such patients might be.

Types of Cases Included. This study was confined to 69 cases of hyperthyroidism showing evidence of gross disturbance in the cardiovascular apparatus. In every instance a subtotal thyroidectomy was performed. There were 51 females and 18 males. The average age was 50.7 years when they first came under observation, and the entire group was followed for an average of 4.5 years. The preoperative basal metabolic rate before administration of Lugol's solution averaged +51.1 per cent; after operation the average metabolism of the entire series was +4.8 per cent.

Peabody^{9,10,11} and others^{12,13} have shown that the basal metabolism in severe grades of heart disease is variable, frequently being normal, but in some instances being elevated to +20 per cent or even more. In heart disease, generally, Peabody states⁹ that "The rise in basal metabolism is neither a constant nor particularly significant feature." We feel that metabolism readings found repeatedly in the neighborhood of +20 to +30 per cent in a patient with heart disease are suggestive of an underlying hyperthyroidism.

In this series all patients with congestive heart failure and angina pectoris as well as hyperthyroidism were included. In the former group the majority had objective evidence of circulatory congestion

such as subcutaneous edema, engorged liver or moisture in the lungs. In a small number there was sufficient dyspnea and cardiac enlargement to make it clear that congestive failure, although not marked, was present. Auricular fibrillation was present in many of these cases, but in none was it the only criterion of cardiac involvement. An analysis of these cases quickly shows that most of them had various forms of heart disease in addition to hyperthyroidism. In fact, there were 15 patients with definite and 4 with questionable mitral stenosis of rheumatic origin. Two cases had aortic insufficiency, 1 being due to syphilis and the other to rheumatism; 35 had hypertension. In 30 cases persistent auricular fibrillation was present, transient in 14 other cases. There were 6 instances of auricular flutter, 1 of bundle branch block, 1 of Adams-Stokes attacks resulting from long sinus pauses and 1 of acute pulmonary edema. Some of the cases naturally fell into more than one group, as a patient could have hypertension, auricular fibrillation and mitral stenosis in addition to hyperthyroidism.

It is interesting that having limited our cases to those with congestive or anginal heart failure, all of the cases, with rare exceptions, presented evidence of other forms of heart disease in addition to hyperthyroidism. Hyperthyroidism alone did not account for the cardiovascular changes in the great majority of the cases. Other factors, such as hypertension, mitral stenosis, etc., combined with hyperthyroidism to produce the abnormal cardiac states in the patients, and these findings persisted after the hyperthyroidism was relieved, although the symptoms may have either improved or disappeared. The above features and the fact that congestive heart failure is extremely rare in young people with hyperthyroidism makes us concur with the prevailing conception that hyperthyroidism itself does not produce heart failure.^{1,3,6,14,15} Of the entire group of 69 patients there were 43 who had objective evidence of congestive heart failure of varying extent. Those with mild congestive failure had merely râles in the lungs in addition to dyspnea; the more marked had gross anasarca. There were 9 who had typical angina pectoris, and 2 of these had had definite attacks of coronary thrombosis a short while before subtotal thyroidectomy. All the remainder had appreciable dyspnea and cardiac enlargement apart from the common complaints found in hyperthyroidism, such as palpitation, weakness, nervousness and sweatings, although they did not show evidence of peripheral congestion. Of this latter group 6 had persistent auricular fibrillation and 5 paroxysmal auricular fibrillation. It is obvious that this group does not include the ordinary type of exophthalmic goiter or those cases of hyperthyroidism in which the heart shows no appreciable evidence of involvement.

Observations on the Blood Pressure. As has been shown by Hurxthal,¹⁶ there is only slight change in the blood pressure following

subtotal thyroidectomy in cases of hyperthyroidism. In his study there was an average drop of 10 mm. in the systolic pressure and a rise of 7 mm. in the diastolic pressure in a group of 46 cases of toxic goiter followed for 12 months after operation.

In the cases studied here similar lack of change was noted. The average readings of 43 of our cases were systolic 153 mm. and diastolic 81 mm. before operation, and systolic 156 mm. and diastolic 85 mm. 3.3 years after operation. The average metabolism determinations at these two times were +45.3 and +5.9 per cent. The group of 20 cases with a normal blood pressure before operation showed an average increase of 10 mm. in systolic pressure after 3.3 years (Table 1). The cases varied considerably as far as the blood pressure readings were concerned. In some instances it was distinctly higher after operation than before, but more often it was slightly lower. It was very rare that a well-marked hypertension before operation entirely disappeared after the basal metabolism was brought to normal by surgery. When this did occur observations made months or years later generally showed return of the hypertension.

TABLE 1.—FOLLOW-UP OBSERVATIONS ON BLOOD PRESSURE.

	Number of cases.	Aver. systolic blood pressure, mm.	Aver. diastolic blood pressure, mm.	Aver. basal metabolic rate, per cent.
Hypertensive:				
Pre-operative	23	179	89	+43.9
Postoperative (3.3 yrs.) . .		177	94	+ 5.1
Nonhypertensive:				
Pre-operative	20	123	71	+46.9
Postoperative (3.3 yrs.) . .		133	75	+ 6.9
Total:				
Pre-operative	43	153	81	+45.3
Postoperative (3.3 yrs.) . .		156	85	+ 5.9

There was a strikingly large number of cases of hypertension among these patients with hyperthyroidism and gross cardiac involvement. There must be more than an accidental relationship between hypertension and hyperthyroidism. It is unlikely that hyperthyroidism itself produces hypertension, inasmuch as restoring the metabolism to normal and relieving the patients of most, if not all, of their symptoms did not significantly alter the blood pressure level. Furthermore there is no relationship between the level of the blood pressure and the level of the metabolism reading either in the same individual at different times or comparing one case with another. Contrariwise, hypertension does not produce hyperthyroidism, for most hypertensives have normal metabolic rates and normal thyroid glands. May it not be that the constitutional type of individual who is likely to get one condition is also apt to get the other, and in this way both necessarily occur frequently together?

If this is true, one may expect to find hypertension occurring with undue frequency in later life in patients who had hyper-

thyroidism with a normal blood pressure in early life. This is borne out by the slight but definite rise in the blood pressure 3.3 years after operation in patients who had pre-operative normal readings.

Hypertension and hyperthyroidism afford frequent practical problems in diagnosis, as many features are common to both conditions. At times it is difficult to tell clinically whether there is any additional hyperthyroidism in a patient who has hypertension, and occasionally even after the results of metabolism determinations are available, the diagnosis still may be in doubt.

Changes in the Size of the Heart. Roentgen ray changes in the size of the heart have been carefully studied in the Lahey Clinic by Hurxthal, Menard and Bogan.¹⁷ They found that the size of the heart in toxic goiter was not appreciably different than in nontoxic goiter when similar age groups were compared. In fact, in their study no relationship could be found between the duration of the disease and the size of the heart. These authors merely call attention to the size of the heart tending to be larger in older patients with coincident cardiovascular disease. Parkinson and Cookson,¹⁸ on the other hand, found cardiac enlargement in 45 per cent of 130 clinical cases of "goiter causing symptoms." They believed that the duration of the symptoms was a factor in producing enlargement. From an experimental point of view, there is reliable evidence that hypertrophy of the heart occurs in animals following the administration of thyroid substances.¹⁹ A study of heart weights in patients dying of hyperthyroidism was made by McEachern and Rake.²⁰ They found that in 27 such cases 16 had cardiac hypertrophy. It cannot be concluded, however, that even in these cases enlargement was due to the hyperthyroidism because a concomitant independent form of heart disease is so frequently present.

In this series of cases there were 10 in which Roentgen ray examination of the heart was made before operation when the metabolism was elevated, and afterward when it was approximately normal. Several other cases were omitted because the difference in the internal transverse diameter of the thorax in the two examinations was too great to make accurate measurements of the heart size possible. The changes in the size of the heart were, on the whole, insignificant. There was only one instance in which the transverse diameter of the heart changed more than 1 cm.; in this case there was a diminution in that diameter of 1.7 cm. In all the others the changes were within the margin of error of the method. The average size of the heart showed a total transverse diameter of 14.3 cm. before operation and a transverse diameter of 14.2 cm. after operation. The internal transverse diameter of the chest averaged 26.2 cm. before and 26.5 cm. after operation (Table 2). Although these data are rather meager, they are suggestive that in "thyrocardias" with gross cardiac involvement, the heart size

will tend to be slightly to moderately increased, that the size does not change to any great extent following operation, and finally that the enlargement itself is due to the coëxistent independent cardiovascular disease rather than to the hyperthyroidism.

TABLE 2.—AVERAGE ROENTGENOGRAPHIC MEASUREMENTS OF THE HEARTS OF 10 HYPERTHYROID PATIENTS WITH HEART DISEASE.

	B.M.R., %	M.R.	M.L.	Tr.	G.V.	Int. diam.	Tr. %, Int. diam.
Just before subtotal thyroidectomy	+41.8	5.1	9.2	14.3	6.4	26.2	54.5
Twelve weeks after operation	- 7.0	5.2	9.0	14.2	6.4	26.5	53.6

Changes in Cardiac Murmurs. There were 27 instances in this series of 69 cases in which specific notation of murmurs was made before and after operation. In all these systolic murmurs of varying intensity were present before operation. In 16 instances the systolic murmur disappeared after operation. In 8 it became less intense and in 3 it remained unchanged. There were 8 of these same 27 that had an additional diastolic murmur. In 6 instances this was apical in origin and the character of the murmur was typical of mitral stenosis. Three of these were first noted after operation. There were 2 cases with aortic diastolic murmurs, 1 of which first appeared after operation. Of 42 cases in which no specific mention of murmurs after operation was made, 27 before operation had only systolic murmurs, 7 had systolic and diastolic murmurs and 1 had only a diastolic murmur at the apex. There were only 7 of the entire 69 who showed no murmurs before operation.

A systolic murmur in these cases, for the most part, was found both at the apex region and at the base of the heart. Although these cases had heart disease besides the element of hyperthyroidism, the frequent disappearance or diminution in intensity of the systolic murmurs makes it clear that hyperthyroidism itself may be wholly or partly responsible for these murmurs. Moreover, the diastolic murmur of mitral stenosis can easily be overlooked, especially during the period of active hyperthyroidism. Furthermore, the ability to hear a diastolic murmur for the first time after operation indicates the importance of careful auscultatory examination when the metabolism has reached normal levels.¹⁴

Changes in the Irregularities of the Heart. Irregularities of the heart in hyperthyroidism are very common. Auricular fibrillation, especially in the transient form, is particularly frequent.* Of these 69 cases there were 32 which had permanently established auricular fibrillation, many of which, no doubt, previously had transient

* See Bibliography, Nos. 1, 2, 3, 5, 7, 8, 14, 21, 22, 23, 24, 25.

attacks of the same arrhythmia. There were additional 12 cases which showed only paroxysmal auricular fibrillation. Inasmuch as a paroxysm of auricular fibrillation is of common occurrence a day or so after subtotal thyroidectomy, cases having such attacks as the only disturbance of rhythm were not included in this group. Ten of the cases of paroxysmal auricular fibrillation never gave any evidence of recurrent attacks after leaving the hospital. There was 1 instance in which transient auricular fibrillation recurred at varying times several years after the operation, but the metabolic rate in this case was found to be elevated and there was additional clinical evidence of mild recurrent hyperthyroidism. One final case had a single transient spell of auricular fibrillation 3 years after operation. This patient had hypertensive heart disease and, because a metabolic rate determination was not made at this particular time, it was uncertain whether or not she had recurrent hyperthyroidism. In a word, there was no instance in which recurrent auricular fibrillation took place in which it was known that the metabolism was normal.

Among the group of 32 patients that had persistent auricular fibrillation there were 24 who were examined at different intervals after leaving the hospital so that one could tell whether or not the fibrillation persisted. Of 11 patients who also had mitral stenosis the irregularity remained established in 10; in the eleventh, normal rhythm was established by the use of quinidin sulphate. Unfortunately this patient suffered an attack of hemiplegia that same day and was for a while desperately ill. Although she made an excellent recovery and the heart has remained regular for almost 2 years, our enthusiasm for the use of quinidin in the presence of mitral stenosis has waned. It is interesting that in none of the 11 patients who had mitral stenosis and persistent auricular fibrillation as well as hyperthyroidism, did the heart return to normal rhythm spontaneously after thyroidectomy. Of the remaining 13 cases the heart spontaneously became regular shortly after operation in 5 without any further medication and normal rhythm has remained for years. One was regularized by the use of quinidin and in the other 7 the auricular fibrillation continued and quinidin was not employed. Of these latter 7 cases, 6 had hypertension and the remaining 1 had a blood pressure of 145 systolic and 80 diastolic with an enlarged heart. No doubt if quinidin had been used in these cases, a regular rhythm might easily have been restored. Some have been followed as long as 8 years and it is known that once the heart became regular transient or permanent fibrillation did not recur during this time.

In summarizing our experiences with auricular fibrillation, one may predict that if the hyperthyroidism is adequately controlled by surgery and the metabolism established at a normal level, cases with transient auricular fibrillation may be expected to be entirely

free from such attacks in a great majority of instances.^{1,2,6,14,22,24,25} Those who have persistent fibrillation and who also show mitral stenosis will almost invariably continue with auricular fibrillation. In some of the others a normal rhythm will be established spontaneously within 1 to 4 weeks after operation. Those in whom regularization does not occur after 1 month will probably continue to show auricular fibrillation indefinitely. For the most part it seems that the irregularity persists because there is present an independent and additional type of heart disease such as hypertension, cardiac hypertrophy or coronary artery disease, although in some the hyperthyroid state still may be lurking despite the partial thyroidectomy. Quinidin may be employed in cases which continue to show irregularity due to auricular fibrillation 1 month after the operation, but we believe there is considerable risk if mitral stenosis is present. It may be added that it is futile to give quinidin for auricular fibrillation before operation and inadvisable for a week or two after operation. In the first instance auricular fibrillation will probably recur promptly, if it disappears at all; and in the second instance, there will be found some cases in which the auricular fibrillation persists for a week or so before spontaneously changing to a normal rhythm.

Paroxysmal auricular flutter occurred in 6 instances in this series.²³ In 5 cases there was no return of such attacks after operation, whereas in 1 case 4 weeks after subtotal thyroidectomy the patient had an attack of auricular flutter which lasted 5 days. The metabolism at this time, however, was +18 per cent. There were no instances of persistent flutter in this entire group.

There were only 6 cases in which it was noted that extrasystoles of one sort or another were present. Of these there were 3 with ventricular premature beats, 1 with auricular premature beats and 2 with nodal beats. No doubt there were other cases in which premature beats occurred which were not noted. Despite this, it is our general impression that extrasystoles are not common in hyperthyroidism. This has been the experience of other writers.^{23,26,30}

Two cases showed an irregularity of the heart due to well-marked sinus pauses. In 1 of these occasional standstill of the heart for from 5 to 8 seconds occurred; this produced fainting and momentary unconsciousness. The heart rate in this case was in the vicinity of 40, and the clinical picture that resulted resembled Adams-Stokes disease, although there was no true auriculoventricular heart block. There were 2 cases that showed first degree heart block or delayed auriculoventricular conduction. In 1 of these the *P-R* interval was 0.23 second before operation and became normal (0.2 second) postoperatively. The second patient had a *P-R* interval of 0.22 second before operation and it was unchanged after operation. Delayed auriculoventricular conduction in cases of toxic goiter has been reported by various writers.^{14,23,26,27} There was

1 instance of block of one of the branches of the bundle of His in our group.

In summary, it may be said that almost any type of cardiac irregularity may occur in "thyrocardiacs" but that the only disturbance that is truly characteristic of hyperthyroidism, and which may frequently disappear after the hyperthyroidism is relieved, is auricular fibrillation, transient or permanent. Sinus pauses may well be due to direct pressure of the thyroid gland on the vagus nerve or on the carotid sinus, for in the case mentioned above both lateral lobes of the thyroid were found at operation to lie posteriorly and behind the trachea in a position that could easily produce such pressure. Most of the other irregularities could result from the accompanying independent heart disease and need not be directly related to the hyperthyroidism.

Effect on Angina Pectoris and Congestive Heart Failure. The association of angina pectoris and hyperthyroidism has been referred to in recent years.^{4,28} The finding of 9 such cases in this series indicates that this association is by no means rare. Although females far outnumber the males among hyperthyroid patients in general, in this group with angina pectoris there were 6 males and 3 females. It is also interesting that at least 7 had typical attacks of angina at rest. This is not at all surprising when it is appreciated that the added drive on the heart in hyperthyroidism is going on constantly. Two of these patients went through typical attacks of acute coronary thrombosis and were subsequently and successfully operated upon for the hyperthyroidism. Although it is difficult to make a comparative analysis between the blood pressure level in these thyroid patients with angina and our "thyrocardiacs" without angina, it seems that hypertension is not as prominent a feature in the former as in the latter. In fact there were several instances in which the blood pressure was perfectly normal.

The clinical improvement that occurred in this group of patients with angina was most striking. The average duration of anginal symptoms in these patients before operation was 31 months. In every instance the attacks either completely disappeared or they recurred very rarely and were much milder. The average length of time these patients were observed postoperatively was 20 months, the interval varying from a few months to about 4 years.

It is our opinion that all these patients were suffering from angina pectoris as a result of the same causes that produce angina in nonhyperthyroid cases. We believe that they have coronary artery disease of varying degrees. In hyperthyroidism the accompanying elevated metabolism merely serves as an added burden so that even while at rest in bed these patients might be compared to a normal individual who is performing some effort. Angina pectoris has been produced following the administration of thyroid medication to patients with myxedema who previously had no such at-

tacks.²⁹ One might say that in the hyperthyroid state these patients were, in effect, exercising 24 hours a day although they were constantly in bed. They might need no additional effort, therefore, to bring on attacks of angina pectoris; in fact, only minor changes in their nervous or physical states might do so. The operation merely relieved them of the added burden on the circulation accompanying the elevation of the metabolism to +35 or +50 per cent, but the underlying process in the coronary arteries, although possibly mild, still remained. It would, therefore, be expected that following the relief subsequent to thyroidectomy, anginal symptoms might still be produced, only now requiring much greater insults, either physical or mental, to produce them and that the progression of the coronary disease would continue with subsequent liability to increase in attacks of angina pectoris. We believe it extremely unlikely that hyperthyroidism itself would cause angina pectoris in a heart otherwise normal, especially one with normal coronary arteries.

In this group of cases there were 43 patients who had physical evidence of varying degrees of congestive heart failure. On the average, one might classify the failure as being moderate to severe. There were many who had general anasarca with peripheral pitting edema, markedly engorged liver, hydrothorax and dyspnea at rest; 11 had mitral stenosis, 1 questionable mitral stenosis and 21 hypertensive heart disease.

There were 2 postoperative deaths. One died within 24 hours after operation in a thyroid crisis during the days before the introduction of Lugol's solution therapy. The other was an instance in which improvement on iodine treatment was so gratifying that both the patient and his physician refused to follow our advice to have a subtotal thyroidectomy performed. It was done some weeks later when the optimum time for surgery had passed. In this case the thyroid condition had been overlooked for 2 years, and the diagnosis of thyroid heart disease, when it was made by one of us, really was accepted with great reluctance on the part of the family physician. In fact, in the entire series of 69 patients there have been no postoperative deaths in cases that were directly under our control since the introduction of Lugol's solution. In most cases the improvement occurred with pre-operative treatment following the use of Lugol's solution and the customary procedures employed in treating heart failure. In these the operation served to maintain the gain previously obtained and enabled such patients to resume approximately normal activities. In others, further improvement took place after operation. It was very striking, except for rare instances, that all evidence of congestive heart failure had disappeared within 2 or 3 weeks following operation.

This group of patients suffering from congestive failure was extraordinary from the fact that so few have died during subsequent

years. The follow-up study of cardiac patients with congestive failure in hospitals no matter what type is analyzed, generally shows a high mortality within 2 years. Here only 6 have died, excluding the 2 postoperative deaths. The average length of life of these 6 patients was 2.5 years after operation. They all had been markedly improved in the meantime. Of the remaining 35 patients the present status of 4 is not known; the average postoperative survival of the others is 49 months. There are 11 who have been alive over 5 years, 6 of whom have survived more than 7 years. Only 8 of these have been followed less than 2 years. The actual length of life after operation, although of itself impressive, is not quite as important as the fact that in almost all instances these patients have been able to resume their ordinary duties.

There are some general impressions that one cannot avoid after a study of any large group of "thyrocardias," such as has been undertaken here. Patients with various forms of heart disease and hyperthyroidism seem to have an extraordinary tenacity for life. Even during the months and years when the thyroid element has been entirely overlooked they carry on better and live longer than one would ordinarily have expected. When they are in advanced heart failure with general anasarca they seem to hold on to life months longer than other patients with heart disease, and it seems that no matter how sick they are, they are still amenable to proper treatment and considerable recovery may be anticipated.

An experience with a single case in this series was quite illuminating. This woman, aged 61 years, had been bedridden for many months with general anasarca. She had been treated with the greatest care by competent consultants and heart specialists. On admission here, cardiac enlargement, auricular fibrillation and moderate hypertension were found. There was no evidence of valve disease. She showed frequent digitalis coupling with nausea on 0.1 gm. of digitalis once or twice a day. The metabolism reading while she had massive generalized edema was +23 per cent; a repeat examination was +18 per cent. On Lugol's solution there was marked improvement and it was decided to perform a subtotal thyroidectomy, notwithstanding the fact that it seemed unlikely that she had true hyperthyroidism. The situation seemed otherwise hopeless and we thought some good might come from subtotal thyroidectomy even if a normal gland were removed. This operation was done and, as a result, she got rid of all the edema, lost 50 or 60 pounds in weight, became ambulatory and felt better than she had for some years, despite the persistent hypertension. The pathologic report was "normal thyroid gland." This, to be sure, was the only instance of the entire series in which the pathologist's report indicated a normal thyroid gland. She continued in good health for 3 years, then gradually developed moderate congestive heart failure again, and finally died 4.5 years after the operation.

The long control period before surgery was undertaken makes it quite unlikely that the marked improvement after operation could have been a coincidence.

An experience like the one cited above makes one suspect, at least, that the removal of a part of the thyroid gland which grossly and microscopically appears normal may be helpful in the treatment of heart failure. Additional evidence that tends to support this view is available. There are patients who have auricular fibrillation who show no other evidence of heart disease nor of thyroid or other disease of the body. Such patients have a normal basal metabolism, no valvular disease or hypertension and are little incapacitated by the auricular fibrillation. We have seen 10 or 12 such cases. They all more or less look alike, have a moist skin and other clinical features resembling those seen in hyperthyroidism but without exophthalmos or an enlarged thyroid gland. Occasionally, years later, such a patient may have an elevated metabolism. Wishart³⁰ has observed 6 of these cases and has reported 1 of them in detail. He concludes that auricular fibrillation (or flutter) may be the earliest detectable sign of thyrotoxicosis in patients with normal basal metabolic rates who later develop Graves' disease. There are reports^{31,32} in which thyroidectomy was performed and the gland found to be hyperplastic when the metabolism was normal.

Morris and Troell,³² in a study of 17 cases of "thyrotoxicosis" with basal metabolic rate within normal limits, found by microscopic examination that the thyroid gland was hyperplastic in 13, with nodular goiter in the remaining 4.

Symmers,³³ moreover, has reported clinical and postmortem observations on 6 cases of "idiopathic cardiopathy," that is, cases in which there was enlargement of the heart, but without valvular, pericardial, arterial, renal or pulmonary causes. At autopsy, however, all of them showed gross and microscopic changes in the thyroid gland; 5 of the 6 were increased in size; microscopic examination of all revealed a "hyperplastic thyroiditis." The basal metabolic rates of these patients were not reported.

The inference from all this is that the metabolism test, even when within normal limits, may not absolutely rule out active hyperthyroidism, or the finding of a normal thyroid gland may not mean that the gland has been functionally normal. Finally, it is possible that partial removal of a normal thyroid gland may be helpful in patients who have either angina pectoris or the congestive type of heart failure.

Summary and Conclusions. 1. A follow-up study was made of 69 "thyrocardiacs" in whom subtotal thyroidectomy was performed. All of these cases before operation had gross evidence of congestive or anginal heart failure. There were 2 postoperative fatalities, and of the remainder the average length of follow-up was 4 to 5

years. Six patients died since the operation after an average survival of 2.5 years. These 6 had been restored either to normal health or to resumption of moderate activities.

2. Forty-three cases had objective evidence of congestive heart failure; 9 had angina pectoris, 2 of whom had had coronary thrombosis; 15 had definite mitral stenosis and 4 had questionable mitral stenosis; 2 had aortic insufficiency (1 was luetic, 1 rheumatic); 35 patients had hypertensive heart disease.

3. The average basal metabolic rate before operation was +51.1 and +4.8 per cent after operation. The average preoperative blood pressure was 153 mm. systolic and 81 mm. diastolic; postoperative, 165 mm. systolic and 85 mm. diastolic. The heart size was practically unchanged as a result of operation. The average pre-operative transverse diameter of the heart in 10 cases was 14.3 cm. and postoperatively it was 14.2 cm. All but 7 of the 69 showed some type of heart murmur before operation.

4. In 27 cases specific notation was made concerning the presence of murmurs before and after operation. All these cases had systolic murmurs and 8 had diastolic murmurs. In 16 instances a pre-operative systolic murmur disappeared, in 8 it became less marked and in 3 it remained unchanged. Of the 8 diastolic murmurs 6 were due to mitral stenosis and 2 to aortic insufficiency. Three of the former and 1 of the latter first became audible postoperatively.

5. Of 32 cases that had established auricular fibrillation, 24 were adequately reexamined. Of these 11 had mitral stenosis and in none of these did the auricular fibrillation spontaneously disappear. Of the remaining 13, 6 reverted to normal rhythm after operation and the cardiac rhythm remained regular for years. There were an additional 11 cases that showed paroxysmal auricular fibrillation. In practically all instances these paroxysms did not recur after the patients left the hospital.

Our experience with quinidin in these cases indicates that it is useless to employ it pre-operatively for auricular fibrillation and dangerous to give it postoperatively to those patients with mitral stenosis and auricular fibrillation. It is best given a few weeks after operation to those without mitral stenosis in whom auricular fibrillation is still persisting.

Six cases of paroxysmal auricular flutter occurred in this series. These attacks disappeared permanently in all but 1 of the cases. In the latter instance there was a single return of this arrhythmia associated with some evidence of persisting hyperthyroidism.

Sinus pauses occurred in 2 patients who were both permanently relieved following operation. There were 2 instances of delayed auriculoventricular conduction, 1 of which became normal after subtotal thyroidectomy.

Extrasystoles were relatively uncommon; there were only 6 instances of this irregularity in the group studied.

6. The great rarity of congestive heart failure in young patients with hyperthyroidism and the almost uniformity of other forms of heart disease (mitral stenosis, hypertension, coronary artery disease, etc.) in those with significant cardiac embarrassment makes it probable that hyperthyroidism is rarely the sole cause of heart failure.

7. The follow-up study of these cases showed that not only was there marked immediate improvement following operation in the various evidences of circulatory embarrassment such as congestive heart failure, angina pectoris and disturbing irregularities of the heart, but the improvement was extremely well maintained.

8. The occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease.

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CLINICAL AND PATHOLOGIC STUDIES IN A CASE OF PURE LIPOID NEPHROSIS.*

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THE existence of pure lipid nephrosis as an entity independent of glomerulonephritis is denied by many authorities on diseases of the kidney. Its extreme rarity is admitted even by those observers who claim for it a separate identity. The studies here reported offer evidence to support the position that lipid nephrosis can occur without demonstrable clinical or pathologic signs of glomerulonephritis. Furthermore, the case record is of interest because the patient was a young adult, whereas most reported instances have been in children; she died relatively early in the course of the disease (9 weeks after onset), without having developed a single clinical indication of glomerulonephritis; and at necropsy the evidence of chronic extrarenal disease which might have accounted for the "nephrotic syndrome" was absent. After careful histologic study of the kidneys including recently advocated staining methods, the glomeruli were regarded as free of the inflammatory or proliferative

* Read before the Section on Medicine of the College of Physicians of Philadelphia, October 24, 1932.

changes of nephritis, although the tubular elements were strikingly altered.

It is necessary in the beginning to indicate exactly what is meant in this report by the term pure lipoid nephrosis. We conceive the term to designate a disease of undetermined etiology characterized clinically by persistent marked albuminuria, massive edema, lipemia and low serum protein; pathologically by kidneys which show lipoid degeneration of the tubules but no inflammatory reaction in the glomeruli insofar as histologic studies can determine. The clinical manifestations of renal irritation or of insufficiency of the kidney as an excretory organ are uniformly absent in lipoid nephrosis. Absent also are cardiovascular disease and chronic infection with amyloid degeneration of organs.

Those who maintain the identity of pure lipoid nephrosis admit that the clinical phenomena may be matched to the smallest detail in both positive and negative aspects by certain stages of glomerulonephritis. The line of differentiation, they contend, is found in the histologic characteristics of the glomerulus: Insofar as the kidney is concerned, lipoid nephrosis is a degenerative process of the tubules, and the glomerulus, unlike that of nephritis, is not detectably involved.

The foregoing position was maintained against opposition by Fahr¹ whose pathologic material and treatment of it have been recognized the world over. The same conclusion is reached by Leiter² in a recent exhaustive review of the subject of nephrosis. Both recognize the great rarity of the disease. Epstein³ originated the conception widely held that the disease is primarily metabolic rather than renal; that in some obscure way the serum proteins are changed and filtered out by normal glomeruli; that the most striking clinical phenomenon, the edema, is due to the tremendous drop in blood protein and consequent loss of colloid osmotic pressure; and that the lipemia is a secondary phenomenon which, if effective, would have regained for the blood a fluid-retaining force.

While most observers agree that the edema of lipoid nephrosis is due to the loss of serum albumin, proof is lacking that the cause of this loss is a change in the protein rather than a change in the glomerulus through which it is filtered. Bell⁴ most recently has consolidated the position of those who believe that all so-called cases of pure nephrosis show some degree at least of glomerulitis, and that the disease is one of the glomerular capillaries. Bell's position is based on: (1) The extremely close similarity to lipoid nephrosis in all respects of the nephrotic type of glomerulonephritis where disease of the glomerulus is obvious; (2) the preponderant evidence⁵ to date that the urine albumin of nephrosis is identical with that of the serum and therefore must be excreted by abnormal glomeruli; and (3) with special staining technique he has satisfied



FIG. 1.—The kidney of lipid nephrosis. It is swollen with marked widening of the cortex.

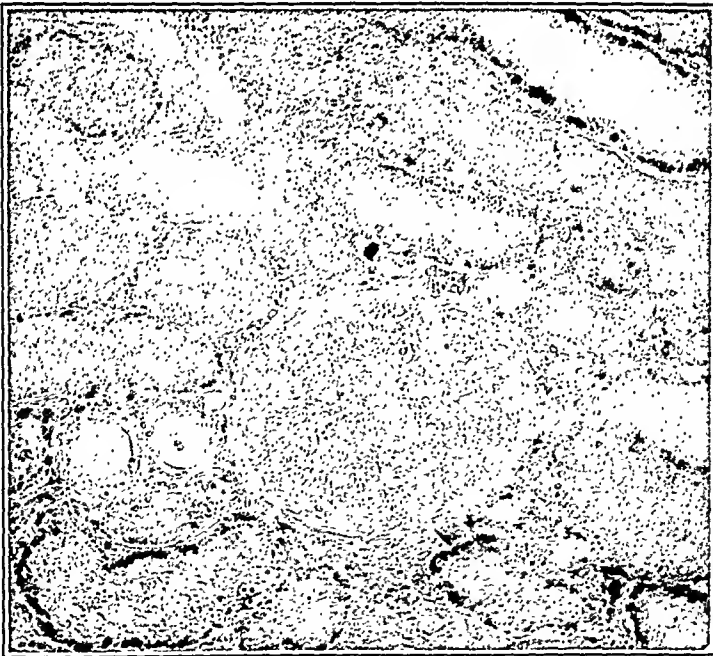


FIG. 2.—Pure lipid nephrosis. Scarlet R stain for fat without counterstain. Complete absence of fat droplets in the glomerulus. Tubules show prominent lipid material. Photomicrograph $\times 175$.



FIG. 3.—Pure lipid nephrosis. There is moderate intertubular edema. A few of the tubular cells can be seen to contain vacuoles. Intratubular casts are prominent. Hematoxylin-eosin stain. Photomicrograph $\times 175$.



FIG. 4.—Pure lipid nephrosis. Glomerular tuft showing no cellular proliferation or obstruction of capillary loops. Azan carmin stain. Photomicrograph $\times 400$.

himself that in "pure" lipid nephrosis there is detectable thickening of the capillary basement membrane and an increase in the number and size of the endothelial cells of the glomerular tuft. The primary disturbance in both nephrosis and nephritis, according to Bell, is an injury to the glomerular capillary by some toxic agent. If little or no reaction occurs in the capillaries a pure nephrosis develops; a moderate reaction produces nephritic symptoms.

Pathologic evidence opposed to the contention that all pure nephrosis cases show glomerulonephritis of some degree is offered in the following case report:

Case Report.—E. G., an American housewife, aged 28 years, complained when first seen at home of 3 weeks of increasing weakness and swelling of the face and extremities. The symptoms began without known cause 9 weeks after the normal termination of her first pregnancy. Midway in the pregnancy her doctor had found a transient albuminuria. No urinalyses had been made in the last 3 weeks before delivery or in the puerperium until she was brought already edematous from her farm home in upstate Pennsylvania to Philadelphia.

The only disease of any consequence in the patient's past had been chorea at the age of 12 years, recurring subsequently in mild abbreviated form on 4 or 5 occasions. The tonsils had been removed at 20 years of age following one of the recurrences. There had been no cardiac symptoms, and shortly before marriage the patient had taken out a small life insurance policy without difficulty.

Physical examination showed edema of the eyelids, lower trunk and extremities, but no excess fluid in the serous cavities of the body. There was no evidence of infection and the temperature was normal. The eyegrounds were negative. The lungs were clear and the heart of normal size and action, with an apical systolic blow well transmitted. Blood pressure readings averaged 115 systolic and 75 diastolic. The abdomen was negative.

Laboratory Findings. The patient refused hospitalization at first and laboratory study of blood and urine was not as complete as desirable. All urine specimens were of specific gravity between 1020 and 1040. When heated, the urine solidified with the coagulated albumin, one quantitative albumin estimation was reported as 50 gm. per liter. Hyalin and granular casts were present in profusion, but microscopic or chemical (benzidin test) hematuria was not detected. The urine contained doubly refractile lipid bodies.

The blood Wassermann reaction and blood count were negative. Blood urea nitrogen (later, after 3 days of urea therapy) was 21 mg. per cent, or barely above normal. Blood serum protein was 4.5 per cent by refractometer, below the level at which edema appears. Blood cholesterol figures were not obtained but the serum was distinctly milky. Kidney function tests proved impossible.

Treatment and Clinical Course. The patient was diagnosed as a case of lipid nephrosis and treated with high-protein diet, limited fluid and salt, thyroid extract and diuretics. Anorexia and increasingly frequent vomiting spells interfered with the diet, but in the intervals, over a period of 4 weeks, the protein intake varied between 70 and 100 gm. daily. The daily urine output varied between 300 and 800 cc. Of the diuretics used to combat the oliguria, ammonium chlorid was not tolerated, urea in 24-gm. daily dosage brought on almost no diuresis. Salyrgan intravenously brought about a transient flushing on 4 of 6 occasions.

The course of the disease was slowly downhill from the beginning, with

no remission worthy of the name. Watery diarrhea, probably caused by intestinal edema, occurred from time to time. A month after she was first seen the patient developed a fever and signs of a cellulitis in the water-logged tissues of the flank, whereupon she was forced to enter the hospital. The end came as a result of the erysipelas-like infection and exhaustion 9 weeks after onset.

Necropsy (U. of Pa. '32-151) (W. T. R.). External examination reveals marked edema, particularly of the abdomen and lower extremities. The right thigh, buttock and flank are cyanotic and the skin is indurated, giving the appearance of cellulitis or erysipelas.

The important internal changes are limited to the *kidneys*. The right weighs 250 gm., the left, 300 gm. The capsule strips easily leaving a smooth surface, yellow in color but free of hemorrhages. The cortex measures 7 to 10 mm. in width and is bright yellow in color in contrast to the medulla which is dusky red, due to hyperemia (Fig. 1). A small wedge-shaped infarct is found in the right kidney. It appears to be recent in origin.

Microscopically the glomeruli are normal in size and there is no recognizable cellular proliferation of either epithelium or endothelium. The capillary tufts are all unobstructed and contain blood. No hyalin fibers are demonstrable by McGregor's stain.⁶ In the capsular spaces there is a network of protein material. None of the cells of the glomeruli contain droplets of lipoid as revealed by the Scarlet R stain (Fig. 2). There is moderate intertubular edema and the tubules themselves are dilated. Many contain casts and cellular debris. The epithelium lining the tubules shows in many places fine vacuoles within the cytoplasm (Fig. 3). The Scarlet R stain reveals these to be lipoid droplets. There is no structural change in the bloodvessels.

Several connective-tissue stains were made: Van Gieson, anilin blue, and orange G, one counterstained with fuchsin and another with azan carmin by the technique of McGregor.⁶ In these sections neither the capsule of Bowman nor the capillary basement membrane showed any thickening. There is no overgrowth of connective tissue (Fig. 4).

Other internal alterations which should be mentioned are the presence of 1600 cc. of milky yellow fluid within the abdomen and a small vegetation measuring 4 or 5 mm. located on the mitral valve of the heart. Microscopically this shows fibroblastic proliferation and a few lymphocytes. On one side the endothelium is lost and a small thrombus was found. No bacteria are present. Postmortem cultures of the subcutaneous tissues in the area of cellulitis, of the heart's blood and peritoneal fluid yielded only an organism of the colon type, undoubtedly a postmortem contamination.

Comment. Although certain clinical data in this case are perforce not complete, we feel that sufficient evidence was obtained to fulfill the rigid criteria for the diagnosis of pure lipoid nephrosis, with pregnancy as a possible exciting factor. In the histologic examination Heidenhain's azan carmin modification of Mallory's anilin blue stain was used according to the technique followed by Bell in his study of nephrosis.⁴

If the view that the glomerular capillary change is primary is correct (*i. e.*, that it is in reality a nephritis), the alterations which permit the escape of albumin are not detectable in this instance by our present-day histologic methods. It is conceivable that the process represents only a change in glomerular capillary permeability for which as yet demonstrable morphologic equivalents are lacking.

Summary. Data are presented from a case which bore the clinical features of lipid nephrosis, and in which the kidneys on careful study showed lipid degeneration of the tubules but no morphologic evidence of glomerulonephritis.

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THE TREATMENT OF PRIMARY DYSMENORRHEA. WITH ESPECIAL REFERENCE TO ORGANO-THERAPY.*

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BEFORE such an organization as this, dedicated as it is to the study of the treatment of disease, no apology should be necessary for the consideration of one of the most difficult therapeutic problems in gynecology. For obvious reasons, and particularly because this affection is commonly relegated to the category of "minor gynecological disorders," it is one of the everyday problems in the work of the general practitioner as well as the specialist. The patients themselves would scarcely acquiesce in its designation as a minor disorder, for it is, in the aggregate, the cause of more suffering and invalidism than many conditions dignified by the appellation of "major."

While the earlier literature is full of articles upon primary dysmenorrhea, almost nothing of solid nature can be crystallized out from them, for they are almost altogether of a speculative nature, both as to the etiology and the therapeutic measures recommended. Only within the past few years, with the intensive study of the physiology of the female reproductive system, has there appeared a hope of solving the problem of the mechanism and the treatment of this extremely common ailment.

* Read at annual meeting, American Therapeutic Society, Baltimore, May 17, 1932.

With the secondary type of dysmenorrhea, associated as it is with some definitely recognizable pelvic abnormality, an explanation of the menstrual pain is usually evident, and the indication for treatment clear. With the primary variety, and it is with this alone that we are concerned in this paper, the pelvic organs are characteristically normal, although the patient may suffer excruciating menstrual pain. Most often, although not invariably, this begins 1 or 2 days before the actual menstrual onset, and ceases after menstrual bleeding is well established, usually after the first day. As is well known, the affection is most often seen in young unmarried women or in married nulliparæ.

While this paper is concerned chiefly with the therapeutic aspects of this problem, these are so utterly dependent upon etiology that the latter must at least be touched upon, the reader being referred, for a full discussion of this question, to a recent paper by the present author, in collaboration with S. M. R. Reynolds. The time-honored view, of course, is that the dysmenorrhea is the result of an obstruction to the exit of menstrual blood, most often because of a kink associated with ante flexion. There are many reasons why this can not explain most cases, not the least being the frequent observation of severe dysmenorrhea without ante flexion or obstruction of any kind and, vice versa, of very sharp ante flexion with no pain whatsoever.

Equally unsatisfactory is the evidence for the importance of hypoplasia of the uterus as a cause of primary dysmenorrhea. For example, a large proportion of dysmenorrheic patients date the onset of the menstrual pain, not from puberty, but from a period several, or perhaps many, years later. This observation is hard to check up with the essential importance of a primary hypoplasia of the organs, present from birth. Furthermore, the uterus of the dysmenorrheic patient is often quite normal in size.

Not so easily dismissed, however, are two other factors, the constitutional and the psychogenic. The first of these will unquestionably explain a certain proportion of cases, just as it will explain the production or exaggeration of other subjective symptoms. Here we apparently have to deal with a lowering of the threshold of pain, so that the normally slight menstrual discomfort is magnified into an actual dysmenorrhea. Most often the constitutional depravity is obvious, or is readily enough revealed by the proper examination. It may be a severe anemia, or tuberculosis, diabetes or any one of many other systemic disorders. In the strict sense, therefore, the dysmenorrhea in such patients is secondary rather than primary, although the pelvic organs themselves are normal. Certain it is that many such patients can be relieved of the dysmenorrhea by correction of the underlying cause, with the institution of proper hygiene, exercise and other indicated measures.

Even more important, although much more difficult to evaluate,

is the psychogenic factor which is undoubtedly concerned in many cases of primary dysmenorrhea, as with other functional disorders. Indeed, there are some gynecologists who believe that all cases are of psychogenic origin, a generalization to which I can not subscribe. Such authors lay much stress upon Freudian factors, but explain other cases as due to such causes as mental shocks at or near the menstrual period, with the subsequent development of a conditioned-reflex mechanism; suggestibility, as when a girl has been reared in the same household with a dysmenorrheic mother; a feeling of repulsion at the offensiveness of the menstrual discharge, and so on.

I am personally convinced that the psychogenic factor is the important one in a considerable number of cases, but I feel just as strongly that it can not explain all. Every gynecologist must encounter patients in whom no such factor can be brought out, who perhaps are of a very phlegmatic temperament, and who apparently possess normal bodies and minds. Psychiatrists with whom I have talked tell me that the assumption of a universal psychogenic factor in the explanation of primary dysmenorrhea would be far-fetched.

Still another factor remains to be considered, that of a possible rôle of certain endocrinopathies. Dysmenorrhea may at times, of course, be encountered in patients with well-defined endocrine disorders, but most often it is not. There have, of course, been many speculative attempts to explain this affection on an endocrine basis, but until very recently nothing of a scientific nature had been contributed. Recent investigations upon the question of the hormonal regulation of uterine contractility have yielded the first results which seem applicable to the clinical problem of dysmenorrhea. The very nature of the pain in these cases would, of course, suggest an origin in an exaggerated or disordered contractility of the uterine musculature. The recent investigations of Knaus, Reynolds and a number of others throw much light upon this problem. They are fully discussed in the recent paper of Novak and Reynolds, based on the latter's studies on the variations in uterine contractility under various conditions, and under the influence of certain hormone factors.

To summarize these only very sketchily, Reynolds has found, by an ingenious method of study, that (1) uterine muscle exhibits a normal rhythm of contraction; (2) all uterine contractions disappear after castration; (3) they are restored by the injection of folliculin; (4) the folliculin-produced contractions are inhibited by the injection of progesterin or of the urine of pregnant women; (5) the normal excitant of uterine contractility is the follicle hormone, while the corpus luteum principle, progesterin, is an inhibitor.

We have attempted to apply these results to the problem of primary dysmenorrhea, always, of course, bearing in mind the possible contributory rôle of psychic and other such factors, as already

discussed. The corpus luteum normally begins to retrogress a day or two before menstruation; in other words, at just the time the dysmenorrhea commonly begins. The natural assumption, therefore, would be that it is the rather abrupt withdrawal of the inhibitory progestin influence which allows full play to the stimulating folliculin. The latter, according to the studies of Frank and others, is present in the blood in increasing amounts from the end of one menstrual period to the beginning of the next. After the formation of the corpus luteum, and especially during the premenstrual period, when it reaches the maximum, the characteristic folliculin effect upon the uterine musculature is inhibited by the progestin produced by the corpus luteum. The withdrawal of this inhibiting effect is apparently responsible for the onset of uterine contractility, and this, in some cases, is characterized by pain.

The above statements are based upon, and I believe are in accord with, the physiological facts which I have summarized. The sequence of physiological events, however, occurs in all women during the normal menstrual cycle, and yet only a comparatively small proportion suffer pain. For this, two explanations suggest themselves. One is that the exaggerated uterine motility is registered as pain only in those women whose pain threshold is lowered by constitutional, psychogenic or other factors. The other is that there must be in some women an imbalance between the two antagonistic hormonal principles, either quantitative or chronologic.

This point is still beyond proof, but I believe that such physiologic investigations as those above mentioned point to a hormonal disorder of uterine contractility as at least the immediate cause of primary dysmenorrhea.

Treatment. The management of cases of primary dysmenorrhea must obviously be directed toward two objectives: (1) the treatment of the attacks themselves and (2) the permanent relief of the condition. These will be discussed in at least a brief and summarizing fashion.

The Dysmenorrheic Attack Itself. When confronted with a patient suffering the often excruciating pains of primary dysmenorrhea, the physician's immediate concern is with the relief of pain. The first injunction to be borne in mind, perhaps, is to refrain from the administration of morphin, for not a few women addicts date their affliction from the use of morphin for this condition. Alcohol should be prescribed with equal caution. While of undoubted benefit, in the form of either whisky or of some of the alcohol-laden proprietaries, there is danger in its use. Cases of moderate severity are, of course, often relieved by the simpler analgesics, such as codein or the coal-tar products, together with rest in bed, hot applications and hot drinks.

From what has been said as to the causative rôle of exaggerated and painful muscle contraction, the administration of antispasmodic

drugs would seem to be called for. The best of these, in my experience, is atropin sulphate, as I discussed in a paper published 17 years ago. This is administered by mouth in doses sufficient to cause mild saturation symptoms. An average dosage is $\frac{1}{120}$ gr. of the sulphate every 4 hours, beginning from a day to several days before the period, depending on the usual time of onset of pain. In a large proportion of cases, great and often complete relief is obtained.

However, such physiologic considerations as I have discussed in this paper suggest that a more rational and perhaps more effective antispasmodic may now be available. The biologic inhibitors of uterine contractility, on the basis of laboratory investigations, are progesterin and the luteinizing principle of the urine of pregnant women. The former is not available for human use, but the latter is, even commercially. Its use I believe to be rational, and the short experience I have thus far had with it is most gratifying. I shall not stress the point now, for the method is too new to speak of results, especially since we are dealing with a disorder where the subjective factor may so readily mislead us.

For those who may be interested in such clinical experimentation, however, I may say that an intramuscular injection of 100 rat units of the substance (Antuitrin S, of Parke, Davis & Co.) is given 1 or 2 days before menstruation, this being repeated 1 or 2 days, depending on the severity and usual duration of the pain. This plan, as I shall again emphasize, constitutes only a part of the intelligent treatment of dysmenorrhea.

Measures Looking to Permanent Relief. The time-honored view that primary dysmenorrhea is cured by the first pregnancy is, in the main, correct, although some exceptions are encountered. Marriage, however, cannot be prescribed as complacently as can medicine.

The factor of hypoplasia, considered so important by some gynecologists, and undoubtedly present in some cases, can, I believe, be helped by the use of theelin. Indeed, I know of no other intelligent method of accomplishing this. The administration of theelin to animals brings about marked overgrowth of the uterus, with hyperemia. With full allowance for the uncertainties and probable inadequacy of dosage for the human, the hypodermic use of folliculin is indicated in primary dysmenorrhea. The administration of 50 rat units on alternate days for 6 days, beginning just after menstruation, is the usual plan I have followed. In other words, all the injections are given during the follicular phase of the cycle.

The resort to cervical dilatation, so common in the past and even at the present day, is of course based on the older idea of the obstructive etiology of dysmenorrhea, now rather generally abandoned. That it has been effective in at least a fraction of the cases permits of no doubt, but the doubt arises in trying to determine the mechanism of its effect. Is it entirely psychic, or is it based upon

a real virtue in the dilatation? One cannot be dogmatic, but there can be little question that in many cases the operation is a form of psychotherapy, at times successful, although not infrequently only temporarily. This is not a radical statement, for it can be made of many other measures which have been used for this condition and, as a matter of fact, there is no doubt that many cases of the "psychogenic" variety are cured without either drugs or surgery.

With reference to this last group the physician should never forget that the psychic factor must always be borne in mind, so that a careful history should be obtained, especially as to the time of onset of the dysmenorrhea, and a possible correlation of this event with a psychic trauma of one sort or another. As already stated, I do not believe that such an etiology can be demonstrated with the constancy claimed by some authors, but not infrequently it can. Furthermore, whatever the cause of the first attack may be, there is always the possibility that the factor of fear may lead to recurrence and perpetuation of the symptom. This subject is as involved as are many other psychiatric problems, but a good history, interpreted along broad and sane lines, will usually lead to a proper evaluation of the individual case.

Every such gynecologic consultation should be an educational one from the standpoint of the patient, the physician taking the time to reassure her as to the significance and normality of the menstrual function, of the fact that it is commonly associated with very little discomfort, that it should cause little or no interference with her usual activities, and so on. I have always felt that in many instances the mothers of dysmenorrheic young girls are in greater need of such education than the patients themselves, for too often the girl at puberty is coddled into the belief that the menstrual period is a time of semi-invalidism and physical discomfort, requiring abstinence from exercise of all sorts and almost a species of segregation. This picture is not overdrawn, although in recent years a far healthier attitude is gradually coming to prevail.

Finally, only an additional word need be added as to the importance of general constitutional building-up and measures of general hygiene. This topic need not be elaborated, although it is an important one. I have repeatedly seen dysmenorrhea disappear entirely, with no direct treatment of the pelvic disorder in itself, by encouraging the patient to get interested in outdoor sports, and engendering in her mind a pride in her physical development.

Summary. The treatment of primary dysmenorrhea, still a baffling problem in gynecology, has been rendered difficult because of our ignorance of the factors concerned in its etiology. Constitutional and psychogenic factors, among others discussed in the paper, would appear to be of prime importance in many cases. Evidence has been brought forward, chiefly from recent physiologic investigations, to indicate that the immediate cause of the pain is

an exaggerated contractility of the uterus, manifested as pain if the pain threshold is lowered, or if there is an actual imbalance between the two hormones which appear to regulate this contractility. These are folliculin, the normal stimulant of uterine excitability, and progesterin, the normal inhibitor. While we cannot, of course, discuss these relationships in a precise or quantitative way, the clinical characteristics of primary dysmenorrhea, on the one hand, and physiologic studies on the other, both indicate the importance of this hormonal factor in the production of the pain.

The treatment of the attack itself, aside from such customary measures as rest, hot applications and analgesics, may rationally include the administration of antispasmodics, such as atropin. Even more intelligent would seem, the administration of biologic uterine antispasmodics, the one suggesting itself being the luteinizing principle obtained from the urine of pregnant women. This substance, readily available, has been shown to be, like progesterin, a powerful inhibitor of the rhythmic contractility of the uterine muscle.

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DEFECTIVE COLOR VISION AND ITS HANDICAPS IN MEDICINE.*

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GEORGE WILSON, of Edinburgh, was stirred to a study of color blindness by the mistakes made by students in his laboratory in judging the colors of chemical precipitates. Among his cases there were 5 physicians. One of them confessed that "red in the lips, cheeks, nose, roses, gooseberries, inflammations and the like looks blue to me! On one occasion I could not tell a blue line of water color drawn across my finger from blood." Another admitted that "a rose, the lips, a ruddy complexion and the face of a man discolored by nitrate of silver are to my eyes absolutely the same."¹

Wilson ventured to say from his experiences that for some of these physicians there could not be such things as "scarlet fever" or "cyanosis." Their defect rendered them incapable of recogniz-

* Aided by a grant from the J. Ewing Mears Research Fund.

ing these conditions. The truth of this assertion was well confirmed in the course of the present work.

Scope of Investigation. Since inspection is one of the chief methods of observation in medicine, whether at the bedside or in the laboratory, and much of inspection is dependent on color perception, it struck us as well worth while to investigate whether or not defects in color perception did materially affect the interpretation of clinical findings.

In this paper the term "color blind" will be strictly avoided in designating those individuals with subnormal color sense. The term should be reserved for those who cannot see any colors at all. In other words, to those who cannot see in the solar spectrum but different gradations of white, gray and black. Such individuals are rare. Between them and those with normal color sense there is a group (from 4 to 10 per cent of the population, according to different authors) who have varying qualitative and quantitative degrees of color sense loss. We will refer to these as having a defective color sense or simply as "color defective." As a generic term this fits our present purposes better than the subdivision into dichromat, trichromat, etc.

Method and Material. The material for this study consisted of 70 members of the junior class of the medical school. In order to sort out the men who had any difficulty in color sense, the entire group was asked individually to read the Ishihara plates.² These plates are modeled somewhat after the original Stilling plates. One of us (L. M. T.) tried the relative merits in a large group of individuals of the Ishihara test, the Holmgren woolens, the Williams lantern and the Jennings test in detecting defects in color sense. The first of these was found to be the most sensitive. The Ishihara test has also the advantage of eliminating from consideration those who are merely "color ignorant" as the subject is required only to read numbers and not to give the names of colors. Clark³ considers it the most successful of the various color blindness tests.

Of the 70 who were given the test, 61 read the plates correctly; 9 read incorrectly 2 or more plates, that is, 12.8 per cent of individuals with color sense defects were found in this group.

The 9 who did not pass the test were then asked to perform the following: (1) Titrate an unknown acid mixture, using phenolsulphonephthalein as an indicator; (2) determine the percentage of phenolsulphonephthalein in 2 urine specimens by matching them against standards of known percentage; (3) identify Gram-negative and Gram-positive organisms in separate smears; (4) describe the appearance of acid-fast organisms in 2 slides, 1 with methylene blue, another with Bismarck brown as counterstains; (5) identify a polymorphonuclear neutrophil, basophil and eosinophil in 3 slides; (6) name the colors of the solar spectrum as seen through a spectro-scope.

TABLE 1.—ANALYSIS OF COLOR TESTS IN 9 DEFECTIVES AND 2 NORMALS.

Subject.	Titration of acid mixture with phenolphthalein as indicator.		Matching 2 urine spec. against P.S.P. standards.		Identification of							Naming of spectrum colors.
	Unknown. Cc.	Titration. Cc.	First. Per cent.	Second. Per cent.	Gram-pos. organisms.	Gram-neg. organisms.	Acid-fast bacilli with methylene bl. as counterstain.	Acid-fast bacilli with Bismarck brown as counterstain.	Polymorph. neutrophil.	Polymorph. eosinophil.	Polymorph. basophil.	
A . . .	1.1	1.1	50 to 60	20 to 25	Correct	Called Gram-pos.	Blue bac. on blue field	Black bac. on br. field	Neutrophil	Basophil	Basophil	Red, yel., gr., blue, pur.
B . . .	1.2	1.2	50 to 55	20 to 25	Correct	Called Gram-pos.	Deep blue bac. on lt. blue field	Blue bac. on golden br. field	Neutrophil	Eosinophil	Basophil	Red, yel., gr., blue, deep blue.
C . . .	1.0	1.0	55	25	Correct	Correct	Dark blue bac. on lt. blue field	Blue bac. on straw field	Basophil	Basophil or neutrophil	Basophil	Red, yel., gr., pur.
D . . .	1.1	1.1	50 to 55	20 to 25	Correct	Called Gram-pos.	Dark blue bac. on blue field	Pink bac. on yellow field	Neutrophil	Probably an eosinophil	Basophil	Red, or., yel., gr., blue, violet.
E . . .	1.3	1.3	50 to 55	20 to 25	Correct	Called Gram-pos.	Entire field and bac. look blue	Dark brown bac. on br. field	Neutrophil	Neutrophil	Basophil	Red, yel., gr., blue.
F . . .	1.1	1.1	50	20	Correct	Called Gram-pos.	Purple bac., blue field	Dark brown bac. on orange field	Neutrophil ?	Neutrophil	Basophil	Red, yel., or., gr., pink, blue.
G . . .	1.2	1.2	50	15	Correct	Called Gram-pos.	Field and bac. look blue	Violet bac. on orange field	Neutrophil ?	Neutrophil	Basophil	Br., yel., red, blue, violet.
H . . .	1.5	1.5	40	10	Correct	Called Gram-pos.	Blue bac. on blue field	Blue bac. on orange field	Basophil	Neutrophil	Eosinophil	Yel., blue.
I . . .	1.3	1.3	30	10	Called Gram-pos. (dark blue)	Called Gram-neg. (green color)	Blue bac. on blue field	Blue bac. on orange field	Eosinophil or neutrophils	Eosinophil	Lymphocyte	Red, yel., gr., blue.
J . . .	1.4	1.4	60	25	Correct	Correct	Lt. red bac. on bl. field	Red. bac. on brown field	Neutrophil	Eosinophil	Basophil	Red, or., yel., gr., bl., pur.
K . . .	1.3	1.3	55 to 60	25 to 30	Correct	Correct	Red bac. on blue mucus	Red bac. on brown field	Neutrophil	Eosinophil	Basophil	Red, or., yel., gr., bl., pur.

The test objects were all typical examples of their kind. The tests were carried out at the same place, at approximately the same time of the day, and with an equal amount of illumination. Any communication between the subjects was prevented. Six students of the same class in school with normal color vision, who had made no mistakes reading the Ishihara plates, were given the tests and used as controls. The results are detailed in Table 1. For the sake of brevity only 2 normals (J and K) are included in the tabulation.

Results. The 9 students who had failed in reading the Ishihara plates also failed in the tests. In the control group an occasional mistake was made in the titration of the acid mixture, which was subsequently corrected when the titration was repeated. The same opportunity for repeating titrations was afforded the color defective group. Occasionally one of the normals would underestimate or overestimate the phenolsulphonephthalein percentage by 5 or 10 per cent, or would fail to name the orange in the spectral colors. No other mistakes were made by the normal group.

Titration by the color defective group were invariably correct. In matching phenolsulphonephthalein specimens, mistakes were frequently made. There was greater underestimation among those with a severe grade of defective color perception (G, H and I). Those with a mild degree of defect made correct or nearly correct matches. One man stated that it was impossible for him to match the specimens, as the standards and the specimens were of different color.

The identification of Gram-positive organisms was made correctly by all the men. All but 2 of the defective group called the Gram-negative organisms positive; 1 of these stated that he could tell the difference between the two kinds because the Gram-positive organisms appeared dark blue, the others green.

The entire group failed to describe correctly the appearance of acid-fast bacilli, if methylene blue was used as the counterstain; no contrast whatever was detected between the organism itself and the surrounding matter. Whenever Bismarck brown was used as the counterstain the contrast was evident and the organism recognized. One man (D), who had seen the organism dark blue against a blue background, saw it in its right shade of pink when Bismarck brown was used.

In the identification of granulocytes, but 2 individuals made correct observations. There was particular difficulty in the identification of eosinophils, as we anticipated.

The naming of the spectrum colors gave us a rough qualitative idea of the color defect of these individuals. It can be seen readily that of the subnormal group, the last 4 probably had the greatest degree of color defect.

To extend the scope of this investigation, each individual was

asked to state some of the difficulties he experienced in color perception during his stay in medical school. The results were interesting. Three men stated they experienced difficulty in detecting skin lesions, especially the mild exanthematous type. Several cases of scarlet fever with a frank rash were demonstrated, but not recognized. A jaundiced patient appeared tan to 1 man, who stated he could be sure of seeing jaundice only when he could contrast it against the white of the sclera. The same individual also had trouble in recognizing cyanosis. Cyanosis, he stated, appeared deep red to him. Once he was shown a patient with carcinoma of the stomach, who was slightly wasted and was told to note the pasty, grayish appearance of the man's face. Although this was obvious to others, the man's color to him was a normal tan.

One man had great difficulty in estimating hemoglobin with a Dare apparatus. The standards, he said, were not strong enough. He stated that he realized he had a defect in color vision, but that he was careful to have his worked checked by a classmate. This classmate was later tested and found to be as color defective as himself. In volunteering information as to other color defective individuals in his class, he pointed out one that he considered particularly severe. This man was tested and found normal. Another student was shown a blood smear of pernicious anemia and instructed to note the difference in the staining qualities of the erythrocytes. Some, he was told, stained light red, whereas others were bluish gray. He countered by saying that all the erythrocytes he saw looked bluish gray and none light red.

One had been shown a culture of *Streptococcus viridans* and could not understand why the organism was called green producing, since the material did not look green to him.

Nearly all of the subjects had difficulty in identifying the tubercle bacillus. This had led to mistakes in the examinations and a few of the men had, in some courses, been given low grades because of their inability to identify this organism. Some had devised ingenious ways of circumventing the difficulty. When doing a test involving the detection of a certain color, one man prepared solutions with a known amount of the chemical for which he was testing. Then he would set them aside and use them as standards while going through with the titration of the unknown.

One of the students (H) became so confused in the coloring of his anatomic drawings that he had a classmate point out to him the colors of the different pencils. He then gave to each one a separate number, made out a table of the colors and its corresponding numbers and always referred to it before coloring any section of his drawing.

Comment. It is evident that color defective perception is an important variable in the estimation of laboratory and clinical

results. Many otherwise unexplained discrepancies between results in different laboratories handling portions of the same material may be explained in terms of difference in color perception. Many of the complicated chemical tests depend for their interpretation upon a keen color sense that sometimes even the normally endowed individual fails to possess from lack of proper education. Likewise, the recognition of certain types of tissue depends upon their staining reaction, and defects in color perception may affect this recognition. The fact that laboratory work is performed, in many instances, by female technicians is fortunate, as it is known that color defective perception is rare in that sex. It might, of course, be argued that in comparing scientific data, a margin of error must, in the last analysis, be considered, owing to the variable "personal equation." A large share of the variability of this equation can, however, be ascribed to differences in color perception.

Although slight degrees of defective color sense should not be set forth as a bar to the study of medicine, the individual with such a defect should be well appraised of it in order that he may make the proper allowance and not engage in lines of work in which he would be distinctly handicapped.

Individuals with the degree of color sense loss as found in G, H and I should be barred from performing laboratory work or specializing in dermatology or in any other specialty in which accurate observation by inspection is essential.

The color defective has, however, as a compensation for his shortcomings in differentiating colors, a high degree of ability in the discrimination of fine brightness values. Many of these individuals see better in the dark than those with normal color vision. Little⁴ mentions a Philadelphia publishing firm which prized one of its color defective engravers very highly for his superiority over workers with normal color sense in transcribing accurately light and shade effects.

This quality, which often leads the color defective astray when identifying colors, should prove advantageous in roentgenology, particularly in fluoroscopic work and the reading of Roentgen ray films. This specialty, therefore, would seem singularly well suited to individuals with the more severe grades of defective color vision.

Summary. 1. Seventy junior medical students were tested for defective color vision. Nine were found defective (12.8 per cent).

2. The 9 students with defective color sense performed tasks requiring color discrimination. All made mistakes, some showing a greater degree of color defect than others. Six students with normal color vision were used as controls.

3. A few of the students had a marked degree of defect in color sense that led to errors in their clinical work.

4. Individuals with markedly defective color sense should be dissuaded from lines of work requiring accurate observation and

encouraged to engage in work calling for technical rather than diagnostic skill.

5. On account of the tendency for good discrimination of brightness values, roentgenology would seem an appropriate specialty for those with a markedly defective color sense.

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ANNULAR PANCREAS.

A COMPILATION OF 40 CASES, WITH A REPORT OF A NEW CASE.

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ANNULAR pancreas is a comparatively rare developmental anomaly, in which the second portion of the duodenum is encircled by a ring of pancreatic tissue. It has both a clinical and anatomical importance. A search of the available literature revealed 39 previously reported cases to which the author desires to add another:

Case History (136089).—A married woman, aged 37 years, was admitted to the San Francisco Hospital, October 14, 1930, complaining of pain in the abdomen for 3 days. She had not felt well for the past few months, had lost 6 pounds in weight, was tired, had been drinking alcoholics heavily, and had noticed that the whites of her eyes had become yellow. Three days previous to admission she was suddenly seized with acute severe pain in the pit of her stomach, not accompanied by nausea or vomiting. The pain continued, and on the following day she vomited a large amount of chocolate-colored fluid which contained flecks of bright red blood, and her stools were black. She had not eaten since the acute attack and stated that she "ached all over."

Family History. Her father died at 82 of "cirrhosis;" her mother of cancer of the uterus at 47. One brother drowned, 2 brothers and 6 sisters were living and well.

Personal History. The patient had the usual childhood diseases, also diphtheria at 32. She had been married twice, but had separated from each husband; both had been heavy drinkers. She was operated upon for appendicitis in 1907, and for adhesions in 1908. In 1909 she had leucorrhea and pelvic inflammatory disease, following which both tubes and one ovary were removed. Her appetite had always been irregular, and she had had

Essential Microscopic Findings. Stomach. The mucosa was markedly atrophic with the outer portion of the glands devoid of epithelium, areas of necrosis, heavy layers of mucus, and no lymphoid tissue. The submucosa and muscular layers were normal. *Liver:* Fatty infiltration, degeneration, and necrosis of the liver cells were marked about the centers of the lobules, with only small remnants of normal cells peripherally. The central areas of necrosis were filled with delicate vascular fibrous tissue in which were fusiform cells containing brown granular pigment and a moderate number of lymphocytes. *Kidney:* There were a few small cortical scars, marked cloudy swelling of the tubular epithelium, with small areas of necrosis and a large amount of granular material in the tubules and glomerular spaces. *Pancreas:* Sections from the head, the tail and the annular portion were all normal pancreatic tissue.

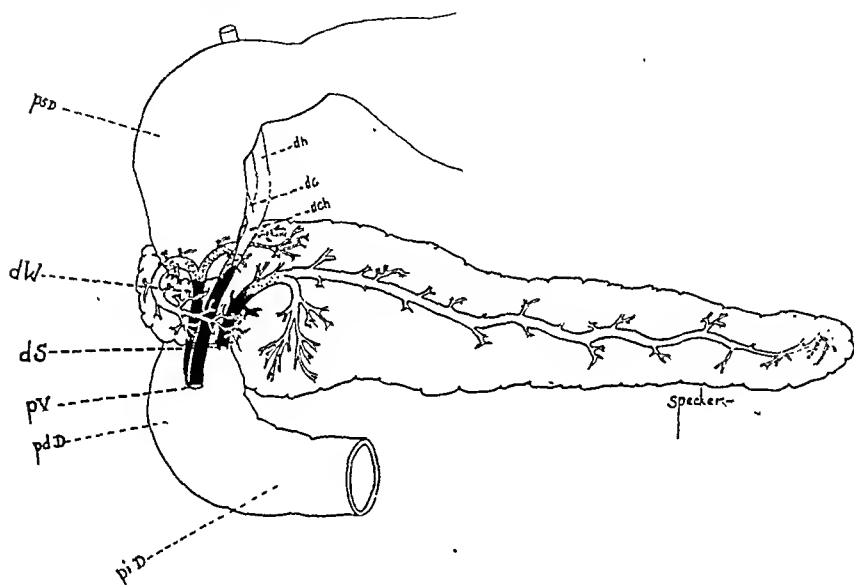


FIG. 2.—Diagram of the arrangement of the ducts in the author's case of annular pancreas. *psD*, pars superior duodeni; *dW*, ductus Wirsungi; *dS*, ductus Santorini; *pV*, papilla of Vater; *pdD*, pars descendens duodeni; *piD*, pars inferior duodeni; *dh*, ductus hepaticus; *dc*, ductus cysticus; *dch*, ductus choledochus.

Anatomical Diagnosis: 1, Chronic alcoholism; 2, chronic gastritis; 3, cirrhosis, early subacute; 4, jaundice, toxic; 5, fatty liver; 6, hemorrhage, gastrointestinal tract; 7, congenital malformation of pancreas (annular pancreas); 8, operations, cholecystectomy, salpingectomy, oöphorectomy, appendectomy, healed; 9, chronic cervicitis; 10, chronic, adhesive, local peritonitis.

Discussion of Literature. Embryologists¹ state that the human pancreas arises in the embryo as two entirely distinct entodermal outgrowths, known as the dorsal and ventral anlagen respectively. The dorsal anlage grows out from the dorsal wall of the intestinal tube, slightly above the level of the common bile duct. The ventral anlage grows in the inferior angle formed by the hepatic diverticulum, and the intestine, and may be more or less bi-lobed. As the

ventral and dorsal anlagen elongate, rotation of the stomach and elongation of the bile duct cause the ventral anlage to approach the dorsal, and ultimately unite with it as diagrammatically shown in Figs. 3 and 4.

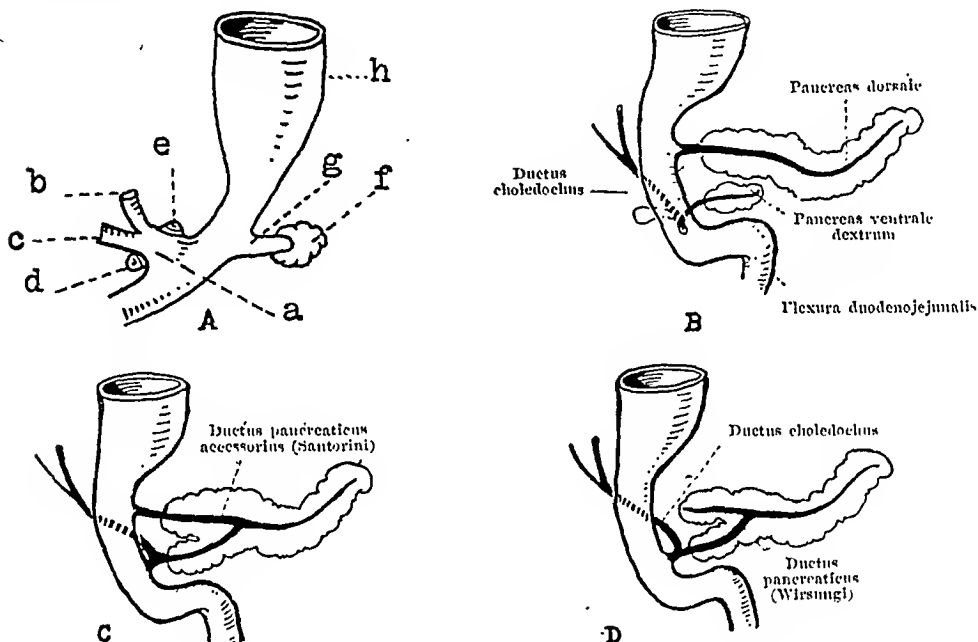


FIG. 3.—Diagrammatic development of the pancreas. A, the early pancreatic buds: a, common bile duct; b, hepatic duct; c, cystic duct; d, right, and e, left ventral pancreatic anlagen; f, dorsal pancreas and its duct; g, h, stomach. (After Piersol.²) B, C, D, the normal migration of the ventral to fuse with the dorsal anlage, the establishment of the pancreatic duct of Wirsung which empties through the duodenal papilla in common with the ductus choledochus. (After Corning in Braus.³)

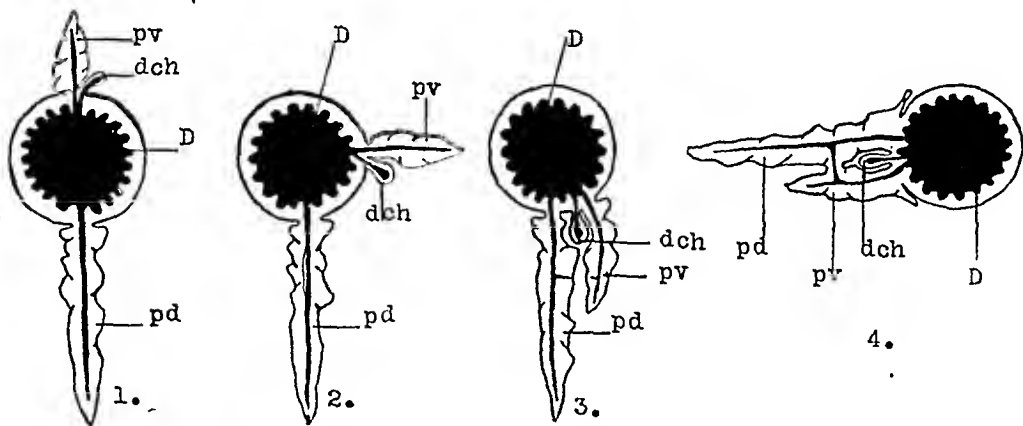


FIG. 4.—Diagrammatic representation of the normal migration of the ventral pancreatic anlage, pv, to fuse with the dorsal anlage, pd, enclosing the ductus choledochus, dch, between them. The anastomosis of the ducts is shown in 4, D, duodenum. (After Lecco.⁴)

The dorsal anlage is larger than the ventral, and grows across the body toward the left, until it reaches the spleen. It gives rise to

the body, the tail and the ventral portion of the head of the adult gland. Its duct opens into the duodenum above the orifice of the common bile duct, and usually anastomoses with the ventral duct. Its outlet persists as the accessory pancreatic duct of Santorini (Fig. 3, C).

The ventral anlage forms a part of the head and more or less of the uncinate process of the pancreas. The duct of the ventral portion usually ends in the duodenum, close beside or in the common bile duct near its duodenal orifice. This ventral duct by an anastomosis with the duct of the dorsal pancreas becomes the outlet of the main pancreatic duct of Wirsung (Fig. 3, D). It will be noted that a large part of the dorsal pancreatic duct extending through the body and tail becomes incorporated in this main duct of Wirsung, and that the ventral pancreas supplies only the outlet.

Should there be any interference in the usual sequence of events, certain anomalies result. Opie⁵ and Simkins⁶ have described marked variations in the pancreatic ducts, hence it is not surprising that the gland itself presents anomalies of development. Simpson⁷ collected 150 cases of aberrant pancreatic tissue, and offered Warthin's explanation as the most plausible. "It is probable that accessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine either upward or downward." "Pancreas minus" describes a condition in which a portion of the pancreas is separated from the remainder by a more marked depression than usual. "Pancreas divisum" is the partial division of the body of the gland by pressure from the vessels during development but the parts are still connected by means of their ducts to the chief excretory channel of the organ. There are instances of nonunion of the ventral and dorsal anlages, so that the duct of the dorsal pancreas persists as the main duct opening into the duodenum at a normally situated papilla minor. At times there is a growth of the glandular substance of the head, so that it partially surrounds the duodenum with a semicircular pancreatic process. The complete encircling of the duodenum with pancreatic tissue is known as "annular pancreas." Gruber⁸ quoted Schirmer⁹ as giving Tiedemann¹⁰ credit for first recording this anomaly in 1818, Bécourt¹¹ in 1830, and Moyse¹² in 1852. In 1862 Ecker¹³ gave it the name ring or annular pancreas. Table 1 lists all the cases found in the available literature, including the one herein reported; making a total of 40 cases.

Tieken¹⁴ suggested two possible theories to explain the annular pancreas: (1) "If the ventral and dorsal diverticulum did not unite as they normally do, but each developed independently, there would be pancreatic tissue on either side of the intestine, and as growth proceeded, the bowel would soon be completely

surrounded by glandular tissue." (2) "In the semiannular type, the condition might be due to an overdevelopment of the head, which sends out processes, partially surrounding the bowel; if this hypertrophy should continue until the processes meet on opposite sides of the duodenum, there would be a true annular pancreas." Symington's¹⁵ case suggested this second theory, and Brines¹⁶ favored it.

Baldwin¹⁷ stated "It is a significant fact that the specimens of annular pancreas which have been dissected show a duct traversing the ring and joining dorsally with the main pancreatic duct, not emptying into the accessory duct. This seems to indicate that this ring of tissue is either a persistence of the left half of the ventral anlage, or an excessive growth from the right half of the same anlage. If it is this latter case, the excessive growth has taken place ventral

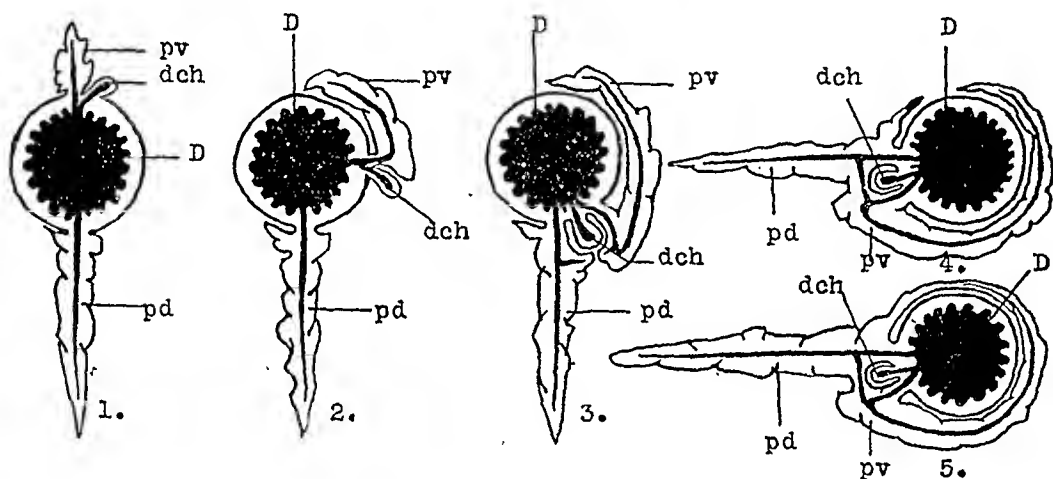


FIG. 5.—Diagrammatic representation of the mode of development of the annular pancreas. The free end of the ventral pancreatic anlage, *pv*, becomes fixed so that during its subsequent migration, with the rotation of the duodenum, *D*, toward the dorsal anlage, *pd*, it is drawn out. With the fusion as shown in 5 it comes to surround the duodenum. (After Lecco.)

to the duodenum, and to the left, at the time that the remainder of the same half was growing or being carried dorsally to ultimately fuse with the head of the gland."

Lecco⁴ believes that the annular pancreas differs from the normal gland only in the ring-forming portion which arises from the dorsal portion of the head of the pancreas. The arrangements of the ducts are comparable to those of the normal pancreas. He does not believe that the ring can be explained by simple hypertrophy, but that it owes its origin to an anomaly of the ventral pancreatic anlage, the tip of which becomes adherent to the duodenal wall, and in the normal migration it is stretched to form the ring. Fig. 5 as suggested by Lecco graphically explains his theory. Cords¹⁸ and Smetana¹⁹ also adhere to the embryonic theory, that the ring portion arises from the ventral anlage.

TABLE 1.—COMPILATION OF REPORTED CASES OF ANNULAR PANCREAS.

Reporter.	Date.	Age.	Sex.	Signs and symptoms.	Location (portion of duodenum.)	Constriction of duodenum. +	Dilatation of duodenum above the ring.	Condition of stomach.	Course of duct in the ring.	Operation.	Other congenital defects.
1. Tiedemann ¹⁰	1818
2. Récaurth ¹¹	1830
3. Noyes ¹²	1832
4. Ecker ¹³	1892	"Young man"	M.	Second	+	+	o. i. m. d.	Bicuspid valve defect.
5. Auberg ¹⁴	1896	"Adult"	M.	Fourth	+	+	"Nothing unusual"
6. Symington ¹⁵	1895	37	M.	Second	+	+	Dil. and hyper.	o. i. m. d.
7. Genesick ¹⁶	1890	M.	Second	+	+
8. Thacker ¹⁷	1893	M.	Second	+	+
9. Sanders ¹⁸	1897	70	M.	Second	+	+
10. Sumner ¹⁹	1900	M.	Second	+	+	Hyper. al. dil.	"Normal"
11. Teken ¹⁴	1901	34	M.	None	Second	+	+	Normal
12. Vidal ²⁰	1905	3 days	..	Vom., visible peristalsis	Second	+	+
13. Santos ²¹	1906	26	F.	Epig. pain, vom. food retcn.	Second	+	Dil., 2 ulcers	Post. gastro-enterostomy; recov.	Duod. atresia.
14. Orl ²²	1909	F.	Second	++	+	Gastroenterostomy; death
15. Leray ²³	1910	46	F.	Gast. upsets (24 years); liquid food 3 mos., right epigastrio resist., belching, const.	Second	++	+	Gastroenterostomy
16. Baldwin ²⁴	1910	Second	+	=	Normal	o. i. m. d.
17. Lecco ²⁵	1910	Second	+	+	"
18. Lecco ²⁶	1910	Second	+	+	"
19. Corley ²⁷	1911	"Smile"	M.	Second	+	+	"
20. Benedict ²⁸	1920	"Soldier"	M.	Ac. intest. obstruo.	Second	++	+	Dilated	Duod. divertic.
21. Gruber ²⁹	1920	58	M.	Second	++	+	"Normal"

	1922	4 mos.	M.	None		+	+	o. i. duod. ab. and post. to ampulla; (m.d.o. with bile duct into ampulla)	Intervent. septum defect; patent for. ovale and duct art.; Meckel's divertic.; umbil. and ing. hernia; horiz. and vert. process besides ring of pane.
22. Bell ²⁰				None	Second	+	+
23. Priesel ²¹	1923	70	M.	Second	+	+	Formed m. d.
24. Anderson ²¹	1923	M.
25. Kurozawa ²²	1923	14	M.
26. Kurozawa	1923	64	M.
27. Susukida ²³	1924	31	F.
28. Shibata ²⁴	1924	M.	Second	+	+	o. i. m. d.	Curv. of spine; duod. divertic.
29. Key ²⁵	1924	"Old"	F.	+	+	Anal atresia.
30. Sugawara-Shibata ²⁶	1925	Fetus 8 mos.	M.	+	+
31. Hennes ²⁷	1928	5 days	M.	Bloody stools	Second	+	+	Emptied chiefly into accessory duod.; small portion i. m. d.
32. Thürl ²⁸	1929	66	M.	None	Second	+	+	o. i. m. d.
33. Smetana ¹⁹	1929	1 mo.	M.	Second	+	+	Anal atresia; club foot; cleft palate; undescended testes; aphasia l. kidney and ureter.
34. Smetana	1928	70	M.	None	Second	+	+	"
35. Smetana	1929	74	M.	Vom., const., abd. pain	Second	+	+	"	Gastroenteros- tony; death
36. Howard ¹¹	1930	46	F.	Ac. pain in R. U. Q., vom.	Second	+	+	o. i. m. d.?	Release of pano. ring; recov.
37. Brines ¹⁰	1930	35	M.	Coffee-ground vom., R. U. Q. rigidity, tender., const., collapse	Second	+	+	o. i. m. d.	Explor. laparot. death, ac. hem. pane.
38. Ehlers ¹²	1930	25	F.	None	Second	+	+	"
39. Brines ¹³	1931	44	M.	Epig. pain, belching, vom.	Second	+	+	Gastroenteros- tony; death
40. McNaught	1932	37	F.	Indig. for years; ac. epig. pain, tarry stools, mod. rigid. R. U. Q., coffee-ground vom. recent	Second	+	+	"	None	Redundant cecum.

* o. i. m. d. = opened into main duet.

The specimen in Bell's²⁰ case resembled the pancreas of a cat, in that it had a horizontal and a vertical process, and in addition an annular pancreas. The position of the pancreatic ducts in this specimen indicated that the annular part developed from the dorsal anlage, inasmuch as its duct opened into the lesser ampulla, while the ducts from the "split pancreas" opened into the ampulla of Vater along with the common bile duct. There were so many congenital malformations associated with this case that it must not be considered on the same basis as most of the other cases. The cases reported by Ecker,¹³ Thatcher,²¹ Vidal,²² Cords,¹⁸ Keyl,²³ and Smetana¹⁹ were associated with some degree of congenital malformation. Keyl suggested that the congenital curvature of the spine in his case may have played a part in compressing the duodenum and displacing the anlagen.

Discussion of Cases. The clinical significance of annular pancreas is readily seen in Table 1, where practically all carefully described cases showed more or less constriction of the second portion of the duodenum, with varying degrees of dilatation of the proximal portion of the small bowel, pylorus and stomach. Specific statements as to the patient's abdominal signs and symptoms were given in only 15 of the 40 cases. In 9 of the 15 (60 per cent) signs and symptoms of high intestinal obstruction were present in varying degrees, hence annular pancreas must be recognized as a clinical entity and considered in all cases presenting such symptoms. In other cases the anomaly was an accidental finding at autopsy or in the dissecting room. Several cases were not reported in detail but were described merely as anatomical curiosities. The fact that the ages ranged from fetal life to 74 years indicates that it is possible to live the normal span of life with this anomaly without serious consequence. The danger lies in the fact that conditions causing swelling of the pancreatic ring, such as hemorrhage, pancreatitis, tumor, hypertrophy, etc. may rapidly bring on acute intestinal obstruction.

Seven of the 40 cases of annular pancreas were operated upon due to upper abdominal signs and symptoms. Gastroenterostomy was the chosen procedure in 5. Howard⁴¹ recommended duodeno-jejunosomy after observing the stormy convalescence following the severing of the pancreatic ring in his case with the accompanying cyst and sinus formation.

Fifty-seven and a half per cent of the reported cases of annular pancreas were found in males, 17.5 per cent in females and in 25 per cent the sex was not given. This probably has no significance since there are usually more male than female cadavers in the dissecting rooms and among the cases autopsied. In the 9 cases with definite upper abdominal signs and symptoms, 4 were males, 4 females and in 1 the sex was not mentioned.

In 88 per cent of the cases in which the arrangement of the ducts was clearly stated, the duct of the ring portion was a part of the

main pancreatic duct of Wirsung. This is a strong indication that the annular portion is a developmental anomaly of the ventral pancreatic anlage.

In the author's case, gastric and duodenal irritation due to alcoholism which caused edema and congestion of the mucosa thus increasing the constriction of the duodenum at the pancreatic ring, combined with cirrhosis and adhesions, was probably responsible for some of the signs and symptoms.

Summary. 1. An additional case of annular pancreas is reported along with a compilation of other reported cases, bringing the total number up to 40. These few cases probably reflect less than the true incidence of this condition; but it is hoped that by directing attention to these the annular pancreas may receive its proper place as a clinical and anatomical entity.

2. The bulk of the evidence indicates that annular pancreas is a developmental anomaly of the ventral pancreatic anlage. It usually causes constriction of the second portion of the duodenum.

3. It has produced signs and symptoms of high intestinal obstruction in a few cases, hence must be recognized as a clinical entity and considered in all such cases.

4. Gastro-enterostomy has been the most favored surgical procedure for annular pancreas.

5. This anomaly has been reported in individuals ranging from fetal life to 74 years of age.

6. Of the reported cases 57.5 per cent have been in males, 17.5 per cent in females and in 25 per cent the sex was not given. This probably has no significance.

7. Twenty per cent of the cases were associated with other congenital anomalies.

8. In the author's case, annular pancreas, chronic alcoholism, gastritis, cirrhosis, and adhesions probably combined to cause the clinical signs and symptoms.

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SOME LIMITATIONS IN THE TREATMENT OF CHRONIC PEPTIC ULCER WITH GASTRIC MUCIN.*

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IN a preliminary report published about 1 year ago, Fogelson¹ introduced the use of gastric mucin in the treatment of peptic ulcer. At this time he reported 12 patients who obtained complete relief

* Read at the meeting of the American Gastroenterological Association, Atlantic City, May 2, 1932.

from symptoms within 3 days and remained well for periods of 2 to 5 months. This communication was followed several months later by an account² of equally striking results obtained in a series of 66 out of 68 patients with chronic peptic ulcer, 15 of whom had previously resorted to surgical intervention. Some of these patients remained asymptomatic for as long as 20 months after the inception of mucin therapy. Kim and Ivy³ reported the prevention of ulcer formation in 17 dogs with biliary fistula by feeding 15 gm. of mucin twice daily. Later, Rivers, Vanzant and Essex,⁴ in a study of more than 40 cases treated with mucin reported "very encouraging results . . . in some instances," but in others "no advantage over the present approved method" could be observed. More recently, Fogelson⁵ reported only 7 failures out of a series of 113 patients, of which 56 had been refractory to all other forms of treatment. Atkinson,^{6,7} in a report of 85 cases, including 11 post-operative recurrences, found that his patients became asymptomatic within the average period of 2.2 days. Brown,⁸ in a preliminary report of his study of 37 intractable cases, 21 of which were hospitalized, found that the average patient became asymptomatic within 8 days and in no instance did a recurrence manifest itself. He encountered but 1 failure in this group. His patients were observed for periods as long as 1 year. Coincident with the subjective improvement, Fogelson, Atkinson and Brown noted a considerable gain in weight and a distinct improvement in the hematologic and roentgenologic picture.

Following Fogelson's first favorable report¹ we undertook a careful study of its clinical value. In this report we wish to relate our experiences and point out the advantages and disadvantages over the present orthodox method.

At the outset we determined the effect of mucin and its fractions upon the gastric acidity and compared it with that of a milk and cream mixture. While our results are to be reported in detail elsewhere* a few remarks concerning our findings seem appropriate: Of 13 experiments on 8 patients with peptic ulcer, the achlorhydria following $\frac{1}{2}$ oz. of gastric mucin persisted for from 15 to 90 minutes, not exceeding 30 minutes in the majority, although the total average was 40. The neutralizing capacity of the peptone-phosphate fraction (ash) which constitutes 40 per cent of commercial mucin, plays no inconsiderable rôle in the antacid property of mucin. The mild secretagogue effect originally noted by Fogelson¹ in his Pavlov pouch dogs, and confirmed by Ivy and Kim,⁹ was corroborated by our studies on patients, for of 21 experiments with mucin and its derivatives, a mild or moderate hyperstimulation was observed in 14 (66 per cent). Rivers, Vanzant and Essex^{9,10} reported a marked secretagogue effect in some of their patients and, from supplementary

* Accepted by the Journal of Laboratory and Clinical Medicine.

studies, concluded that it was due to a histamin substance present in certain batches of mucin. A 3 oz. mixture of milk and cream (equal parts) compared favorably with the average achlorhydric response to $\frac{1}{2}$ oz. of gastric mucin but was devoid of secretagogue effect. Although the "modus operandi" of mucin in ulcer therapy does not yet appear to be clear, the latter findings point more to its action as a demulcent than to its acid-combining power, a conclusion in accord with the views more recently expressed by Fogelson⁵ and his collaborators.^{6,7,8}

Clinical Procedure. In each patient a careful detailed anamnesis was procured, especial emphasis being laid upon the response to previous forms of treatment and the duration of remissions. The diagnosis was made by the usual clinical and roentgenologic methods. Only cases of ulcer uncomplicated by other disease were chosen. Gastric mucin was given to 28 patients, of whom 24 had a duodenal ulcer, 1 had a duodenal and a gastric ulcer, 1 a gastric ulcer, 1 a pyloroplasty and 1 a pyloroplasty and gastrojejunostomy. Eight were hospitalized and at rest in bed; the others were ambulatory, being seen in the gastro-intestinal clinic of the Michael Reese Hospital and in private practice. Many of them had in the past received thorough present-day medical supervision and nearly all had derived more or less satisfactory though temporary relief. Many had ulcer symptoms for several years and, having followed various régimes without permanent relief, welcomed any new form of treatment which would ward off an operation. Three additional patients treated with mucin elsewhere are included in our series.

The method of its administration was that at first suggested by Fogelson¹ in his preliminary report. (1 oz. 3 times daily with the meals and 20 to 30 grains in capsules every hour between meals) and later modified after hearing some minor changes advocated by him in a personal communication ($\frac{1}{2}$ oz. 5 times daily between meals and 20 grains in capsules every 2 hours). As further suggested,¹¹ belladonna was given to those who had a pylorospasm. If the capsules of mucin produced epigastric or substernal distress, they were omitted and the powder alone used in increased amounts, thereby compensating for the deficit. When diarrhea occurred, indicating an inability to "digest" such quantities of mucin (Fogelson¹¹), the amount was diminished to the point of individual tolerance and, wherever possible, subsequently increased. In no case had the patient been taking more than 40 grains of alkalies daily before mucin was given.

The diet consisted of milk and cream, cereals, poached or soft boiled eggs, custards, gelatine puddings, cocoa, ice cream, toast and butter, seedless jams and jelly, fruit juices and puréed fruits and vegetables. Boiled or broiled meat was not added until 3 weeks after the patient became symptom-free.

Roentgen ray studies were made every 3 months in order to detect any changes in the ulcer defect.

Results. The results of our experience may be divided into five groups: 1, those refusing to continue mucin; 2, unimproved; 3, improvement and relapse while under treatment; 4, generally improved; 5, miscellaneous.

1. **PATIENTS REFUSING TO CONTINUE MUCIN.** Table 1 shows that 6 patients discontinued the use of mucin within a period of 1 to 7 days. In 2, intense nausea precluded its administration beyond 1 day and 1 week respectively. In 4, nausea accompanied by vomiting appeared. In 1 of these repeated vomiting followed the first and only dose, while in another retention vomiting occurred every evening, the vomitus containing many undigested capsules together with large quantities of mucin. On the seventh day he developed constant intense boring pain indicative of a penetrating lesion. In 3 the predominating symptoms of pain or heartburn or both became intensified and in 2 of these nausea and vomiting were associated, profuse vomiting 6 hours later giving complete relief in 1. In all of these patients substitution of alkalis for mucin effected immediate relief from the untoward symptoms and they became totally asymptomatic in a few days. (Wherever alkalis were given it was generally in the form of calcium carbonate, or occasionally sodium bicarbonate, 10 grains 3 times daily.)

TABLE 1.—PATIENTS REFUSING TO CONTINUE TREATMENT.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Reason for stopping mucin.
S. L.	42	M	10 yrs.	1 wk.	Increase of pain; relief with Pfunder's* tablets.
E. D.	46	M	20 yrs.	1 day	Severe pyrosis shortly after mucin; slight relief with soda; complete relief after profuse vomiting 6 hrs. later; nausea.
B. M.	27	M	2 yrs.	2 days	Intense nausea; vomiting.
H. L.	34	F	5 yrs.	1 dose	Nausea; recurrent vomiting; could not tolerate taste or smell.
M. S.	26	M	4 yrs.	7 days	Nausea; retention vomiting; increased pain; relief with diet and alkalis.
M. K.	42	F	6 yrs.	2 days	Intense nausea.

* The chemists for the American Medical Association reported "that Pfunder's Stomach Tablets apparently contained bismuth subnitrate, 30.5 per cent; magnesium oxide, 22.8 per cent; baking soda, 24.4 per cent."

2. **UNIMPROVED.** Symptoms of these 8 patients (Table 2) had been present for periods ranging between 2 and 13 years. One had previously had an excision of the ulcer with a pyloroplasty and 1 had both a duodenal and a gastric ulcer. Mucin was given for periods of 3 weeks to 3 months, the majority receiving it for 3 to 6 weeks. Three patients manifested a slight diminution in the

intensity and duration of symptoms for 7, 8 and 18 days respectively, only to be followed by a relapse without any further improvement. One of these noted an increased number of stools during the first week.

TABLE 2.—UNIMPROVED.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
S. A.	39	M	5 yrs.	3 wks.	Improved first week; 2 to 3 b. ms. daily; recurrence second week; discontinued after 3 weeks.
J. M.	53	F	"Years"	25 days	Slightly improved first 18 days; then recurrence.
S. D.	34	F	7 yrs.	27 days	Improved first few days; then recurrence.
D. W.	48	M	12 yrs.	4 wks.	Pain and pyrosis worse; heaviness, bloating, vomiting, lost weight; improved with alkalis.
J. S.	41	M	2-3 yrs.	6 wks.	Recurrent pain and pyrosis; longest period of relief—10 days.
B. L.	43	M	7 yrs.	5 wks.	Nausea and vomiting at first, then relief 4 days and recurrence; relief 4 mos. with Pfunder's tablets; recurrence; mucin again; pain and pyrosis worse; Pfunder's tablets 4 days later—relief.
M. B.	34	M	10 yrs.	6 wks.	Epigastric heaviness; frequent vomiting, 6th wk.; increased pain; "better without mucin."
I. B.	48	M	13 yrs.	3 mos.	Epigastric distress worse 1st 4 days; vomiting 7th day (never before); improved next 11 days; then relapse; no improvement after 3 mos.

One patient (D.W.), who was being treated successfully for a gastric ulcer by the use of diet and alkalis, but who still showed a definite though smaller Haudek's niche, was placed on the same diet without alkalis. Three weeks later, his symptoms having recurred, the efficacy of mucin was tested over a period of 4 weeks. The pain and heartburn became worse, heaviness and bloating appeared, he vomited once and in 4 weeks lost $3\frac{1}{2}$ pounds. Maximum doses of belladonna were also tried. Restoration to alkalis (by request of patient) produced immediate and progressive improvement.

In another (B.L.), nausea and vomiting were present during the first 2 days and although mucin was taken for 5 weeks, relief from his ulcer symptoms was noted for only 4 days. He finally resorted to alkalis, derived complete relief in a few days, felt well and ate all types of food for 4 months before he had another recurrence. Mucin was again tried but the symptoms became more severe and more constant. Four days later he voluntarily discontinued mucin and reported immediate relief from alkalis. In the other 2 patients (M.B. and I.B.) mucin apparently intensified the existing symptoms and induced vomiting. One of these discontinued mucin at the end of 6 weeks because of recent repeated vomiting and reported an amelioration of symptoms after the resumption of alkalis.

J. S. complained of bloating after each mucin feeding and noted

alternating relief and recurrence, the longest free interval being 10 days. Mucin was discontinued 6 weeks later on his own accord.

3. IMPROVEMENT AND RELAPSE WHILE TAKING MUCIN. We observed 6 patients who, first manifesting improvement, subsequently developed recurrent symptoms while taking mucin. As shown in Table 3 symptoms had been present periodically for as long as 3 to 16 years. One had a pyloroplasty and a later gastrojejunostomy with evidence of a recurrent ulcer. Mucin was given to this group for 3.5 to 8.5 months, improvement beginning immediately in 4 cases and not until the lapse of 5 to 17 days respectively in 2 others. Improvement continued uninterruptedly for 12 days to 5.5 months and was followed by recrudescences lasting as long as 3 months.

TABLE 3.—IMPROVEMENT AND RELAPSE WHILE TAKING MUCIN.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
J. W.	38	M	5 yrs.	5 mos.	Nausea and heaviness 3 wks.; anorexia; occasional vomiting; improvement began 5th day; alternating relapse and improvement; worry! improvement with belladonna.
J. L.	41	M	5 yrs.	3½ mos.	Immediate relief of pain for 7 wks.; epigastric fullness as before; finally ate everything; pain recurred; diet restricted again; no relief.
H. H.	29	M	8 yrs.	7 mos.	Relief after 17 days; improved 14 wks.; anorexia; stopped mucin (nausea, cramps, diarrhea); recurrence; mucin again, 3 mos.; no relief; colon symptoms returned; operation: 2 duodenal ulcers.
M. R.	40	M	3-4 yrs.	3½ mos.	Immediate moderate improvement for 4 wks.; recurrence, nausea, vomiting, cramps, diarrhea, lost weight; improved with diet and alkalis.
H. R.	43	M	10 yrs.	8½ mos.	Immediate improvement; gained weight; flatulence; 5½ mos. later pain recurred; dosage increased; gradual improvement; 3 mos. later occasional pain.
A. T.	45	M	16 yrs.	4 mos.	Immediate progressive improvement 12 days; then alternating improvement and relapse for 2 mos.; no further improvement; constipation relieved.

When mucin was substituted for alkalis, the diet remaining the same, J. L. (pyloroplasty and gastrojejunostomy) noted immediate relief of pain and subsequently was able to eat a larger variety of foods, although the heaviness and bloating continued to be present after each feeding. A recurrence set in abruptly 7 weeks later with no further response despite dietary restrictions. Remissions of the same or longer duration had been observed previously while on alkalis.

In 2 patients (H. H., M. R.), abdominal cramps, borborygmi and diarrhea appeared 1 to 2 months after mucin was started. In 1 of

these (H. H.), reducing the dosage (to 70 gm.) improved these symptoms, but the constantly recurring nausea constrained him to discontinue mucin. Concomitantly the colon symptoms disappeared, only to reappear when mucin therapy was again attempted. No improvement in the ulcer symptoms was apparent 3 months after renewing the mucin. At operation, soon afterward, 2 active kissing duodenal ulcers were found. In the other patient the diarrhea disappeared following temporary reduction of mucin, but abdominal cramps continued. Later nausea and vomiting appeared during or after each mucin feeding, necessitating supplementary feedings to insure the proper intake (90 gm.). After his relapse had persisted 2.5 months the substitution of alkalis effected an immediate progressive improvement in the ulcer symptoms and a prompt subsidence of the untoward symptoms.

N. O. improved immediately and, except for the flatulence which disappeared as the dosage was reduced to 75 gm. daily, remained well 5.5 months when his symptoms returned. By increasing the mucin to 100 gm. daily he slowly improved but still complained of occasional pain 3 months later. One patient (A. T.) reported gradual improvement for 12 days, followed by short periods of relapse and improvement, finally becoming refractory to further mucin therapy. J. W. manifested a response somewhat similar to the latter, although marked improvement was observed only after maximum doses of belladonna were given. It is noteworthy that most of his recurrences followed periods of great financial stress and strain.

In all of these patients the blood and stool examinations were normal throughout and the weight remained constant. In no instance were we able to detect any improvement in the Roentgen ray appearance of the duodenal bulb. Further, it is pertinent to remark that during the period of observation the dosage of mucin was unaltered except in the cases cited.

4. **GENERALLY IMPROVED.** Seven patients may be relegated to the domain of "generally improved." They had complained of recurrent distress for 10 months to 15 years. To date, as seen from Table 4, 6 have received mucin for 3 to 5 months. One patient became asymptomatic immediately but was not seen after his discharge from the hospital 1 week later.

Immediate improvement was noted in 4 others. Of these, 1 was symptom-free after the 1st day; another after the 4th day, the former manifesting no response to diet and alkalis during the previous 5 weeks, whereas the latter, during an earlier recurrence, had responded to diet alone in 1 week. Of the remaining 2 who improved immediately the relief was more gradual and while recurrences, usually mild and of short duration, occurred in both, the response was distinctly better than that following alkali therapy during previous recurrences.

TABLE 4.—GENERALLY IMPROVED.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
B. S.	42	M	"Years"	4 mos.	Diarrhea, cramps, belching, increased pyrosis for 4 wks.; then improvement of all symptoms on 75 gm. daily with belladonna.
C. D.	34	M	6 yrs.	5 mos.	Gradual improvement; nausea 1st wk.; relapse 5th wk. for 5 days; feels well except occasional pain; gained 5 pounds.
I. D.	24	M	2 yrs.	5 mos.	Immediately improved; 3 recurrences lasting 3-15 days; takes 65 gm. daily; gained 6 pounds.
S. R.	47	M	7 yrs.	3½ mos.	Diarrhea (6 b. ms. daily) and flatulence first few days—disappeared on less mucin (65 gm.); no pain after 4 days; heartburn gradually improving; gained 4 pounds.
I. C.	35	M	2 yrs.	3 mos.	Nausea 1st wk.; anorexia; immediate relief of pain.
M. S.	23	M	10 mos.	4 mos.	Anorexia and increased pyrosis 1st wk.; then progressive improvement; asymptomatic 19th day; diarrhea, lower abdominal pain; no ulcer pain.
R. M.	30	M	15 yrs.	1 wk.	Immediate improvement; did not return.

One patient began to improve on the 7th day and was asymptomatic on the 19th day. Another did not show any improvement until the end of 4 weeks, when belladonna in maximum doses was given. In both, however, the symptoms were intensified at first. The former patient had been on a diet alone for the preceding 2 weeks and the latter on a diet with small daily doses of alkalies for 3 weeks, both without any relief.

Nausea was present for 1 week in 2. Diarrhea, lower abdominal cramps and flatulence appeared in 3, necessitating a constantly reduced dosage (to 65-75 gm. daily) in 2 and making mucin prohibitive in the third (M. S.), although total relief from his ulcer symptoms obtained while taking the mucin.

The weight remained constant in 3, whereas 3 others gained from 2 to 6 pounds. Blood and stool examinations were normal throughout. In no instance was there a disappearance of the duodenal defect, as demonstrated by repeated roentgenologic studies.

5. MISCELLANEOUS. In this group we have included 3 patients who had been treated with mucin elsewhere, but who consulted us relative to a different form of therapy. One discontinued mucin because of the intense nausea which it provoked. Another reported 2 recurrences, the last recurrence persisting for 3.5 months despite large amounts of mucin in conjunction with belladonna. He improved immediately and became asymptomatic within 2 weeks after being placed on the usual milk and cream and alkali régime. The third patient received mucin for 6 months with only slight relief for 2 months, followed by a relapse and no further response. He

had previously visited the Mayo Clinic, where surgery was recommended. Our Roentgen ray studies disclosed a typical clover-leaf deformity. An emergency operation performed a short time later revealed a large perforated duodenal ulcer.

Because we can not justifiably assign his response to any of the aforementioned groups we are including the case of D. F. in this category. Aside from occasional heartburn, his only symptoms were repeated hemorrhages occurring as long as 1.5 years apart. In the interim he was able to eat all forms of food with impunity. We had hoped, therefore, to prevent further hemorrhages by mucin therapy. To date he has taken mucin for 5 months without any apparent hemorrhages. Seven weeks after starting mucin, however, he developed intense epigastric pain, heartburn, belching and repeated vomiting, all of which subsided in 2 weeks. His Roentgen ray films still show a definite duodenal defect.

TABLE 5.—MISCELLANEOUS.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
D. F.	41	M	1½ yrs.	5 mos.	Asymptomatic at outset except for hemorrhages; pain, pyrosis, vomiting, belching 7 wks. after starting mucin, lasted 2 wks.; no recurrent hemorrhages.
M. B.*	42	M	"Years"	6 mos.	Slight improvement 2 mos.; relapse; no further improvement; perforated shortly after.
S. S.*	50	M	5 yrs.	1 wk.	Nausea; discontinued mucin.
W. B.*	34	M	6 yrs.	1 yr.	Relief in 1 wk.; 2 recurrences later while taking mucin; relief by alkalies and diet after persistent symptoms for 3½ mos.

* Treated with mucin (90 to 100 gm. daily) elsewhere.

TABLE 6.—UNTOWARD SYMPTOMS DURING MUCIN THERAPY.

	Refused to continue.	Unimproved.	Improved and relapse.	Improved.	Miscellaneous.	Total.
Symptoms intensified . . .	1	1	..	2	..	4
Nausea	1	..	1	2	2	6
Nausea and vomiting . . .	2	1	2	5
Nausea, vomiting and pain	2	3	1	6
Anorexia	1	2	..	3
Flatulence	3	3	3	1	10
Diarrhea	1	..	1	..	2
Diarrhea and cramps	2	2	..	4

Untoward Symptoms. We have found no report containing a record of the untoward symptoms which may confront the physician. Accordingly we have reviewed our cases from this aspect. Table 6 shows the frequency with which we encountered an intensification

of the prevailing symptoms, anorexia, nausea, vomiting, cramps, diarrhea and flatulence. That these symptoms are of no little importance is evidenced by the fact that by virtue of their presence some patients were compelled to discontinue mucin entirely, even though definite relief had been achieved; others were unwilling to give it an adequate trial and still others had to reduce the dosage, a factor which may have inhibited more striking results in some. In many, epigastric distress was noted for some time after the capsules were swallowed.

Comment. The natural cycle of events experienced by individuals with chronic peptic ulcer, its disposition toward spontaneous remissions lasting for longer or shorter periods of time during which any type of food may be consumed with absolute impunity, recurrences as well as remissions which are antedated by and related to changes in the psyche, as well as other recognized factors must obviously make it extremely difficult to evaluate properly the advantages purported to be derived from any medicament designed for the relief of ulcer symptoms. Further, that a diet consisting of puréed fruits and vegetables and other well comminuted foods, such as Fogelson^{1,2} recommends in the beginning of mucin therapy, will by itself in many cases be conducive to a remission, irrespective of the number of previous recurrences, is a frequent observation. Consequently, we simultaneously observed as controls a group of 15 patients with peptic ulcer of many years' duration, whom we treated by a similar diet, adding alkalies and belladonna wherever indicated. Our results to date have been almost uniformly satisfactory, some becoming asymptomatic immediately. None of them developed alkalosis or other untoward symptoms. Again, in our mucin series we observed several refractory cases which responded immediately to the substitution of alkalies.

It is noteworthy nevertheless that partial or complete symptomatic relief was achieved with mucin in 7 patients who failed to respond to other forms of therapy. Such results indicate that gastric mucin may have a place in the treatment of peptic ulcer, notwithstanding the shortcomings previously discussed as untoward symptoms, although prolonged observation under carefully controlled conditions is essential to the formulation of any definite conclusion. One may not anticipate many cures, however, because of the frequent operative and necropsy findings of larger or smaller penetrations into the pancreas, the intrinsic and extrinsic scar formations, their resultant influence upon the normal physiology of the stomach and especially the duodenum and the impossibility of normal anatomic restitution. At the present writing, then, we should advocate its use in cases refractory to other forms of treatment and as a step toward the evasion of a surgical procedure. In view of the many available proprietary forms of mucin it is important that a preparation free from histamin substances,^{4,10} such

as the one we used, be administered. It is hoped that certain refinements in the manufacture of gastric mucin will ultimately eliminate the untoward symptoms herein recorded.

Conclusions. 1. Gastric mucin probably acts not through its acid-combining power but by virtue of its demulcent effect.

2. Experience with 30 mucin treated patients, as compared with 15 ulcer cases receiving other forms of treatment, shows that some will not continue its use because of the disagreeable taste and certain untoward symptoms. In others, prolonged administration effects no relief, whereas other forms of treatment are successful. In still others, relief is temporary and followed by a relapse. In the remainder relief occurs with mucin when other forms of therapy fail.

3. Further refinements in its manufacture may widen its scope of usefulness in the treatment of peptic ulcer.

NOTE.—We wish to acknowledge our indebtedness to Dr. David Klein of the Wilson Laboratories, who so kindly supplied us with the mucin. We are also grateful for the coöperation extended by the Misses S. Elkin, N. Taylor and D. Elliott of the dietetic department of the Michael Reese Hospital.

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REVIEWS.

MAN AND MEDICINE. By DR. HENRY E. SIGERIST, Professor at the University of Leipzig. Introduction by DR. WILLIAM H. WELCH, Professor of the History of Medicine, The Johns Hopkins University. Translated by Margaret Galt Boise. Pp. 340. New York: W. W. Norton & Co., Inc., 1932. Price, \$4.00.

In his foreword, Professor Welch says "Designed primarily to present in broad outlines a picture of modern medicine, with its historical and cultural background to students entering upon the study of their profession, the interesting character of this presentation, the artistic and orderly arrangement of the subject matter, the clear and flowing literary style, well preserved, in Margaret Boise's translation, the broad principles enunciated and especially the historical treatment makes the work scarcely less welcome to other cultivated readers, both medical and lay."

There is no doubt but that this statement is a happy one, and it reiterates the purpose and intention of the author who says that "This book is intended primarily to acquaint young people who have chosen to enter medicine with the nature of their studies and their future profession. . . . It would please me should the book stir the interest of physicians as well."

We have carefully read the book and enjoyed it immensely, but while doing so, could not help meditating upon the primary purpose as expressed by both author and introducer, and wondering whether its appeal to the graduate who will understand what it is all about and be familiar with the terms and the facts, will not be immensely greater than to the beginner who will no doubt be as astonished at the amazing breadth of the subject he hopes to learn as bewildered by its terminology.

It is quite true that no physician will find the terminology other than simple and commonplace; a well-educated layman will understand it, but a youth just out of college must possess considerable perseverance as well as great interest in medicine if he ever finishes it.

Occasional amusing mistakes in translation occur: one such on page 217 is the confusion of the words "hybrid" and "bastard" that leads to the astounding statement in the last paragraph that "*all humans are bastards.*" But this in no manner diminishes the excellence of the work, for no one incapable of realizing the error will ever read it.

As we have enjoyed and profited by the book ourselves, we are glad to recommend it to others, especially, however, to graduates of medicine.

J. McF.

PSYCHOPATHOLOGY OF FORCED MOVEMENTS AND THE OCULOGYRIC CRISES OF LETHARGIC ENCEPHALITIS, MONOGRAPH SERIES No. 55. By SMITH ELY JELLIFFE, M.D., PH.D., of New York, N. Y. Pp. 219; 26 illustrations. New York: Nervous and Mental Disease Publishing Company, 1932. Price, \$4.00.

INCLUDED in this thesis is an abstract of the more than 200 cases of lethargic encephalitis, reported up to 1931, in which there had occurred the oculogyric crisis. In addition, the author analyzes the 4 cases of patients seen by him in consultation.

The crisis is not an early manifestation of the disease and nearly always it is confined to the Parkinsonian type. The eye spasms may be tonic, clonic or spasms of convergence. The crises may last from a few minutes to one or more days and may occur several times a day or may be a month apart. Certain psychological manifestations usually accompany it: "2. The thought movement is slowed. 3. The emotional state is mostly one of conscious anxious compulsion. 4. Involvement of consciousness (vigilance) varies from slight to marked degrees of involvement." In the final chapter, Psychopathology, is given the Freudian interpretation of these interesting phenomena, supplemented by the author's personal views.

This monograph is a welcome contribution to the literature of lethargic encephalitis. The bibliography is voluminous, mostly foreign, and there is a fair index. N. Y.

THE EXPECTANT MOTHER'S HANDBOOK. By FREDERICK C. IRVING, A.B., M.D., Professor of Obstetrics, Harvard Medical School, etc. Pp. 203; 26 illustrations. New York: Houghton Mifflin Company, 1932. Price, \$1.75.

THIS is an excellent manual on pregnancy for the average woman. The important topics as hygiene, diet, minor complications and danger signals serve as an excellent standard for discussion by the physician of the proper course of life of his maternity cases. The chapter on anesthesia in labor might serve very well to offset some of the hysterical outbursts by lay writers in the past few years. Some of the material in the final chapter on evolution and heredity seems too technical for the average woman. The book is rather sparsely illustrated. A widespread distribution of this book would do much to promote an intelligent interest in maternity problems among the laity. P. W.

CANCER: CIVILIZATION: DEGENERATION. By JOHN COPE. Pp. 293; 55 illustrations. London: H. K. Lewis & Co., Ltd., 1932. Price, 15/- net.

IF the student hopes to find in this book advanced scientific information about *cancer*, he will meet with disappointment, for the author, though a practitioner of medicine, is a philosopher and sociologist, and not a biologist, pathologist or scientific oncologist. His idea is "to go back to the time before the first cancer research laboratory was built and continue the wide methods of investigation then in vogue." This enables him to avoid technicalities and "direct his words to the medical profession in general, and to the educated members of the general public."

But the method involves him in errors, leads to dogmatic statements upon insufficient data, and to conclude his book with philosophical speculations of questionable validity. The work more or less abounds with the familiar but false statement, used, for instance, by Willy Meyer and James Tobey, that "cancer has become one of the most curable of all diseases." Can ignorance account for such a statement or is there an international propaganda in this direction? Whatever the experience of those experts who treat large numbers of "cancer cases" with "great success," it must be remembered that they only meet with that success in carefully selected cases of appropriate types of tumors. With such facts in mind is it not wicked to place before a lay reader, intelligent as he may be, the statement that "cancer has become one of the most curable of all diseases"? It has not! Few cases are cured, and the incidence and death rate continually rise! But the reader soon finds that the only cases that are so "curable"

are "very early cases." Hence a variation of the original propaganda to "come early to get cured." But Cope goes further; the real time to come is before there is a cancer. Use every possible means of preventing it.

The author believes his vital message to be that cancer is caused by *Degeneration*. It, in turn, is the result of disease, inactivity or inadequacy of those organs in which it most frequently develops. This argument is pursued systematically. Degeneration of the jaw, resulting in defective teeth, results from civilization and the change of foods from the tough and gritty bones and nuts ground up by the teeth of our savage ancestors, to the soft "paps" and "porridges" eaten by the spoon-fed youth of the present day. The improved quality of the foods leave no "roughage" for the stomach and intestines to work upon and they also soon "degenerate" with resulting gastro-enteroptosis, appendicitis, ulcers and cancers. Lack of use is the chief cause of the degeneration that results in the cancer. It is interesting to see this argument applied to the organ of sex, and the overwhelming prevalence of cancer of the uterus and breast referred to disuse and consequent degeneration of those organs! A lengthy digression upon sex and its problems, and a somewhat tedious philosophic speculation upon social, moral, political and esthetic decadence somewhat along the lines made familiar by Lothrop Stoddard and Robert Briffault, winds up with the philosophical and sophistical conclusion that "To prevent cancer, therefore, our first object must be to exercise those organs which in the circumstances of our civilization are now being insufficiently used and thus to cause their invigoration and rejuvenation."

To one crushed under the wheel of misfortune, who has just been told that he is the victim of cancer, it is small comfort to learn that it might have been prevented if some thousands of years ago his stone-age ancestors could have been persuaded to continue to eat the same coarse foods, and to breed large families as rapidly as possible. Nor does it appeal strongly to the writer of this review to look hopefully to the future elimination of the disease by having our descendants of some thousands of years hence, revert to the same supposedly more beneficial manners and customs of savagery.

J. McF.

DISEASES OF THE CORONARY ARTERIES (MYOCARDITIS). By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University, etc., and HAROLD LUETH, Ph.D., M.D., Formerly Instructor Physiology, Northwestern University, Chicago. Pp. 164; 42 illustrations, 3 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, \$5.00.

THIS book is the result of the senior author's desire to answer various perplexing questions that have been asked him on the basis of his compiled experiences plus an unbiased review of the literature. Accepting the thesis of Huchard, that the cardiac symptoms of chronic cardiovascular disease are the product of arteriosclerosis of the heart, which is synonymous with chronic myocarditis, he includes "(Myocarditis)" in the title—a point of view which we hope is being increasingly abandoned today. Angina pectoris, dogmatically set down as the result of arteriosclerosis of the coronary arteries in the Introduction, is considered on page 28 *et seq.* from the various customary points of view, the authors apparently concluding that it may be caused by any one of several conditions producing an insufficient blood supply. Chapter II, Physical Examination of the Heart, is concerned chiefly with electrocardiography; Chapter III, Anatomy, entirely with Gross' description of the blood supply. Chapter IV, Pathology, having listed 3 possible causes of interstitial changes in the myocardium (acute

arteritis, toxic or bacterial interstitial proliferation and primary muscle degeneration), discusses *i. a.* Buerger's disease, gumma, infarct, pericarditis. A certain lack of orderly arrangement adds to difficulties of comprehension; thus the summary at the end of Chapter V is found to summarize only part of the chapter; other chapters have no summary; Fig. 42 (an experimentally produced aneurysm in a dog), seems to have landed on p. 151 purely by accident. A list of 213 references should prove useful, though it is by no means exhaustive or even up to date. Thus while the book undoubtedly has its uses, it is disappointingly far from being the help that one might look for.

E. K.

ENGLISH-SPEAKING STUDENTS OF MEDICINE AT THE UNIVERSITY OF LEYDEN.

By R. W. INNES SMITH, M.D. (EDIN.), With Foreword by JOHN D. COMRIE, M.D., F.R.C.P. (EDIN.), Lecturer on the History of Medicine at the University of Edinburgh. Pp. 258; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 16/- net.

To American medicos the University of Leyden should always have an especial interest on account of Boerhaave's great influence, chiefly exerted through the University of Edinburgh and English medicine, on 18th century medicine in this country. This book contains well over 2000 names of English, Scotch, Welsh and Irish students at Leyden, and yet the Reviewer was able to find only a few Americans among them (Cp. "John Adams, the Virginia Americanus, 1794, Med."). This confirms the statement made to the reviewer a few years ago that he was the first American to work in the Boerhaave laboratory at Leyden for more than a century.

Going beyond Peacock's publication in 1882 of an "Index to the English Speaking Students who have Graduated at Leyden University," the present volume not only lists all those who have attended the University but follows (except in the case of the most famous) their subsequent career in a concise manner that conveys a wealth of information in a small space, often derived from almost inaccessible sources. This painstaking work should be not only invaluable to students of medical history but also a stimulus to its readers to visit this charming center of learning. The influence of Leyden was so great for over a century that it was the most sought after resort of those seeking the best in medical education. To-day it not only produces and harbors eminent scholars but preserves to a marked degree the charming atmosphere of its former eminence. The old University building with its Senate Chamber and its adjoining waiting room for the candidates about to be examined ("Hic sudavit sed non frustra"), Boerhaave's "Hortus" and the adjacent shop of the famous Elzevirs are well worth a visit, as those who attended the recent Congress of Medical History there can testify.

E. K.

CALIFORNIA'S MEDICAL STORY. By HENRY HARRIS, M.D., Associate Clinical Professor of Medicine, University of California; Chief of Medical Department, San Francisco Polyclinic. With an Introduction by CHARLES SINGER, M.D., D. Litt., University of London, London, England. Pp. 421; illustrated. San Francisco: J. W. Stacy, Inc., and Springfield, Illinois: Charles C Thomas, 1932. Price, \$7.00.

THE growing list of state medical histories being published in this country, if the additions and standards continue at the present rate, bids fair not only to provide much instructive "local" entertainment, but also to ensure a corpus of American medical history data that would hardly otherwise be

accumulated. This, the latest of the series, has certain novel features that especially commend it to the general (in addition to the local) reader. As Charles Singer points out in the Introduction, "For the study of medical history, California presents quite exceptional advantages. The geographical isolation of its population makes a true local study more valid than would be the case for most states. The earlier records have been better and more lovingly preserved in California than in any other civilization that has developed so recently and so rapidly. The presence of first-class library facilities is unique for so youthful an aggregate. The very rapid evolution of Californian civilization has carried with it a no less rapid evolution of medicine from the primitive and magical to the highly scientific, though no less human, discipline which is enabling the medical schools of the State to provide as well equipped medical men as are to be found anywhere in the world." A good balance has been maintained between readability and documentation, illumined by gleams of humor, which occasionally are at the State's expense. The local taboo of climate is touched upon with humorous satire. The volume has been beautifully prepared by the Grubhorn Press with unusually attractive type and paper. Even the difficult subject matter of the illustrations has been successfully handled. The extensive bibliography and careful indices further add to a splendid production.

E. K.

THE HOUSE THAT FREUD BUILT. By JOSEPH JASTROW, PH.D., LL.D.
Pp. 293. New York: Greenberg, 1932.

THE method of psychoanalysis can hardly have failed to arouse the curiosity if not the active concern of specialists, general practitioners and thoughtful laymen who are impressed by the increasing strain that the complexities and tension of modern life have put on the "psyche" and by the evidence of its increasing failure to stand up under this strain. Attempts to evaluate the psychoanalytic method, however, are made so difficult and the overemphasis of sex has been so repugnant to the average man that the psychoanalytic method today remains about as much *sub judice* as at any time since its discovery 50 years ago. From its very nature the truth of its premises can never be tested, as could the bacterial theory of infectious disease, for instance, and the therapeutic test is notably difficult and fallacious. Holding to the middle course, the author discusses in nontechnical language the pros and cons of this important topic, giving due weight to its achievements and properly discounting its exaggerations. This evaluation then by an unbiased, skillful writer on psychological topics should prove valuable to many.

E. K.

ANESTHESIA. By W. STANLEY SYKES, M.A., M.B. (CANTAB.), D.P.H. (LEEDS), M.R.C.S., Anesthetist to the General Infirmary at Leeds, etc. With a section on Local Anæsthesia by P. J. MOIR, M.C., M.B. (GLASGOW), F.R.C.S. (ENG.), Hon. Assistant Surgeon, General Infirmary at Leeds, etc. Pp. 128; 6 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, \$2.00.

SYKES has crowded into one small book much practical experience concerning inhalation anesthesia. In Part I on "General Principles" he outlines clearly first the essential rules to be followed in the administration of an anesthetic, and then details the psychologic aspect of anesthesia, and the treatment of the various complications that may arise. In Part II on "Methods" he devotes chapters to each of the usual inhalation anesthetics

used in England. Ethyl chlorid, chloroform and the less commonly used anesthetic mixtures are fully discussed, whereas ethylene, avertin and rectal anesthesia are dismissed with a paragraph or two. Part III on Local and Regional Anesthesia is little more than a brief description of the method. The complications and their remedies, so clearly detailed in the first part of the book are conspicuous by their absence in Part III. The book is excellent as a practical handbook for beginners in general anesthesia.

L. F.

THE HEART RATE. By ERNST P. BOAS, M.D., Associate Physician, Mt. Sinai Hospital, New York City and ERNST F. GOLDSCHMIDT, PH.D., Research Fellow (1930-1931), Department of Surgery in the Yale University School of Medicine. Pp. 166; 68 illustrations of figures and charts. Springfield, Illinois: Charles C Thomas, 1932. Price, \$3.50.

BOAS and GOLDSCHMIDT studied the diurnal and nocturnal variations in heart rate by means of the cardiograph, an instrument for the continuous recording of heart beats. Observations were carried out in 103 normal adults over periods of from 12 to 24 hours, showing the variations in heart rate accompanying sleep, exercise, food-taking and various other episodes of daily life. Studies of 27 young boys undertaking exhausting exercise, and of 77 patients undergoing anesthesia and operation are reported. The last chapter consists of observations on "The Heart Rate in Disease." A number of small groups of patients were studied: Hyperthyroidism (10), Neurocirculatory Asthenia (12), Progressive Muscular Dystrophy (7), Poliomyelitis (7), Valvular Disease (9), Active Rheumatic Myocarditis (?), Congestive Heart Failure (?), Arthritis Deformans (?), Auricular Fibrillation (?), and Heart Block (?). (The Question marks indicate that the number of patients is not stated.)

The observations reported in this book are carefully made and of considerable interest. The authors have occasionally been tempted to be a little uncritical in their discussion of the implications of some of their observations.

F. W.

BOOKS RECEIVED.

NEW BOOKS.

Men Against Death. By PAUL DEKRUIF. Pp. 363; illustrated. New York: Harcourt, Brace & Co., 1932. Price, \$3.50.

Physical Chemistry for Students of Biology and Medicine. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 182; 26 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$2.75.

Oral Spirochetes and Related Organisms in Fusospirochetal Disease. By DAVID T. SMITH, A.B., M.D., Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C. Pp. 243; 53 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$4.50.

- A Manual of Embryology.* By J. ERNEST FRAZER, F.R.C.S. (ENG.), Professor of Anatomy in the University of London; Lecturer at the Medical School of St. Mary's Hospital, etc. Pp. 486; 282 illustrations. New York: William Wood & Co., 1932. Price, \$8.00.
- A Guide to Human Parasitology.* By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, etc., and T. SOUTHWELL, D.Sc., PH.D., A.R.C.Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, etc. Pp. 271; 122 illustrations and 2 colored plates. New York: William Wood & Co., 1932. Price, \$4.00.
- Anleitung zur Frühzeitigen Erkennung der Krebskrankheit.* By various contributors. Pp. 134. Leipzig: S. Hirzel, 1932. Price, Rm. 3.-.
- Varicose Veins and Haemorrhoids.* By V. MEISEN, M.D., Former Chief Surgeon to the Polyclinic, Sundby Hospital, Copenhagen. With a Preface by AUG. KROGH, PH.D. Pp. 149; 25 illustrations and 8 colored plates. Copenhagen: Levin & Munksgaard, 1932, and London: Oxford University Press, 1932. (No price given.)
- Non-tropical Sprue.* By TH. E. HESS THAYSEN, M.D., Senior Physician to the St. Elisabeth's Hospital, Copenhagen. Pp. 258; 39 illustrations. Copenhagen: Levin & Munksgaard, 1932, and London: Oxford University Press, 1932. (No price given.)
- Radiologic Maxims.* By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P., Editor, the Radiological Review; Radiologist, Saint Mary's Hospital and Blessing Hospital, Quincy, Ill., etc. With a Foreword by HENRY SCHMITZ, A.M., M.D., LL.D., F.A.C.R., F.A.C.S., Professor of Gynecology and Head of the Department, Loyola University School of Medicine, etc. Pp. 127. Quincy, Ill.: Radiological Review Publishing Company, 1932. Price, \$1.50.
- Experimental Analysis of Development.* By BERNARD DÜRKEN, Professor in the University of Breslau. Translated by H. G. and A. M. NEWTH. Pp. 288; 120 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, \$4.75.
- Habits. Their Making and Unmaking.* By KNIGHT DUNLAP, Professor of Experimental Psychology in the Johns Hopkins University. Pp. 326. New York: Liveright, Inc., 1932. Price, \$3.00.
- Streptococci in Relation to Man in Health and Disease.* By ANNA W. WILLIAMS, M.D., First Assistant Director, Bureau of Laboratories, Department of Health, City of New York. Pp. 260; 7 plates, 1 figure and 19 tables. Baltimore: The Williams & Wilkins Company, 1932. Price, \$5.00.
- Poliomyelitis.* A Survey Made Possible by a Grant from the International Committee for the Study of Infantile Paralysis. Organized by JEREMIAH MILBANK. Pp. 562; 24 plates (1 in color), 82 tables and 19 charts. Baltimore: The Williams & Wilkins Company, 1932. Price, \$6.00.
- The Surgical Clinics of North America, Vol. 12, No. 6 (Philadelphia Number, December, 1932).* Pp. 280; 110 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- The Medical Clinics of North America, Vol. 16, No. 3 (University of California Number, November, 1932).* Pp. 195; 31 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- Growth.* By the late JAMES LORRAIN SMITH, M.D., LL.D., D.Sc., F.R.S., Professor of Pathology, University of Edinburgh. Edited by J. S. HALDANE, C.H., M.D., F.R.S. Pp. 131; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 6/- net.

The 1932 Year Book of Radiology. Diagnosis. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. *Therapeutics.* Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York, etc. Pp. 750; 498 illustrations. Chicago: The Year Book Publishers, Inc., 1932. Price, \$6.00.

Modern Alchemy. By WILLIAM ALBERT NOYES, University of Illinois, and W. ALBERT NOYES, JR., Brown University. Pp. 207; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.00.

The Diagnosis and Treatment of Postural Defects. By WINTHROP MORGAN PHELPS, B.S., M.D., M.A., F.A.C.S., Professor of Orthopedic Surgery, Yale University, etc., and ROBERT J. H. KIPHUTH, Assistant Professor of Physical Education, Yale University, etc. Pp. 180; 107 illustrations, 14 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.00.

NEW EDITIONS.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.), Surgeon to St. Mary's Hospital, Paddington; Senior Surgeon to the Bolingbroke Hospital, Wandsworth Common, etc. Pp. 248; 30 illustrations. Sixth edition. New York: Oxford University Press, 1932. Price, \$3.25.

Outline of Preventive Medicine. Prepared Under the Auspices of The Committee on Public Health Relations, New York Academy of Medicine. By 24 Contributors. Editorial Committee: FREDERIC E. SONDERN, CHARLES GORDON HEYD, and E. H. L. CORWIN. Pp. 462. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1932. Price, \$5.00.

"Following the suggestions made by the reviewer of the book, three new chapters have been added and additional material included in many of the other chapters" (24). (From the Editorial Committee's Introduction.)

A Laboratory Manual of Physiological Chemistry. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, University of Pennsylvania. Pp. 284. Second edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1932. Price, \$2.50.

"It might be emphasized to students using this manual that it is not intended as a reference book. The experiments have been selected to furnish experience and information in the various branches of physiological chemistry. Certain quantitative methods have been chosen from among a large number available on account of their didactic value and the relatively simple outfit of laboratory apparatus required for their execution." (From the Author's Preface.)

A Text-book of Pathology. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, Johns Hopkins University, Baltimore. Pp. 1212; 652 illustrations. Fifth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, \$10.00.

An Introduction to Dermatology. By NORMAN WALKER, K.T., M.D., LL.D., F.R.C.P., Consulting Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Assisted by G. H. PERCIVAL, M.D., Ph.D., F.R.C.P., Assistant Physician. Pp. 382; 100 plates (82 in color) and 92 text illustrations. Ninth edition. New York: William Wood & Co., 1932. Price, \$7.00.

This edition differs from the preceding largely because the therapeutic teachings have been so thoroughly revised—a change made necessary by the many newer methods which have developed in the dermatological field in the past 8 years. Twenty-eight new illustrations and plates have been added, together with three dermatoses which have more recently secured places as dermatologic entities.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Tobacco Sensitiveness in Thromboangiitis Obliterans.—One of the earliest suggestions as to the etiology of thromboangiitis obliterans was that it in some way depended upon the overuse of tobacco. Various other hypotheses have been advanced, such as a specific infection, an endocrine imbalance or a toxic factor being responsible, tobacco being the most frequent toxic agent. Probably there would be a greater belief in the importance of this plant in the etiology of the disorder if it could be shown that all individuals who are so diseased use tobacco, but in many instances of thromboangiitis obliterans the patients have not used tobacco of any kind. The great majority, however, have been heavy smokers. HARKAVY, HEBALD and SILBERT (*Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 104) have recognized the importance of this weed plant in the etiology of thromboangiitis obliterans, and Silbert, particularly, has studied the incidence of the disease in smokers and nonsmokers. He has observed no typical incidence of the disease in men who did not smoke and he likewise has seen clinical improvement in the disease when the use of tobacco was stopped. The question has been further studied by investigating the specific hypersensitivity to tobacco. Sixty-eight cases of the disease were studied, and 122 controls who were heavy smokers. A goodly number of the latter were Russian Jews. Extracts of tobacco were prepared in several ways and five different extracts were tested on every case of thromboangiitis obliterans and every control by the usual methods of testing skin sensitivity. Eighty-three per cent of the cases of thromboangiitis obliterans reacted to one or another of the tobacco extracts with varying degrees of intensity. Of the controls about 10 per cent gave a reaction, none of which was marked. Among the controls were 15 patients who had circulatory disturbances of the lower extremities, arteriosclerotic in character, all of whom were tobacco negative. Among 15 persons suffering from hay fever, all reacted positively to tobacco, whereas only 2 of the 68 patients with thromboangiitis obliterans reacted to ragweed. Fifteen of these patients, however, reacted to other antigens, but in all of them tobacco was the dominant one. From these studies the authors attempt to draw no definite conclusions other

than that a large percentage of the patients suffering from thromboangiitis obliterans are allergic and that this allergy is characterized by hypersensitiveness to tobacco.

The Blood Picture in Exophthalmic Goiter and Its Changes Resulting from Iodin and Operation. A Study by Means of the Supravital Technique.—Ordinary methods that have been used routinely for the past quarter of a century in counting the blood are being supplemented more and more by more highly specialized studies than those used in the past. The introduction of a comparatively simple technique of supravital staining of blood examination has made this possible. An example of these types of studies is seen in the paper by HERTZ and LERMAN (*J. Clin. Invest.*, 1932, 11, 1179), who studied the blood of patients suffering from exophthalmic goiter. They found that the most characteristic and marked alteration from the normal blood picture in patients with exophthalmic goiter consisted in a relative and absolute increase in the number of monocytes, the figure averaging 14.1 as contrasted with the normal average of 5.7. The percentage of lymphocytes was also increased, although the absolute number was normal. Discrepancies of the blood reports of the past have arisen probably from misclassifying monocytes as lymphocytes. The monocytes tend to increase with an increase in the basal metabolic rate, whereas the lymphocytes have a downward tendency as the metabolism rises. After the administration of iodine there occurs a reduction both in the total number and the percentage of polymorphonuclears and a decrease in the lymphocytes. This reduction in the monocytes is proportional to the reduction in the absolute metabolic rate. Operation on the thyroid is followed by an increase in the total number of leukocytes as a result of an increase of polymorphonuclears and monocytes, of which only the percentage of monocytes has changed significantly. After operation, in the final changes in the blood picture it is noted that there is a lowering of the metabolic rate that is proportionately greater than the change in the blood picture. The authors correlate Aschoff's ideas concerning the monocyte of the circulating blood being a part of the reticuloendothelial metabolic apparatus with their own results, hinting that activation of this system occurs in hyperthyroidism and that iodine depression is linked with a depression of the reticuloendothelial system.

SURGERY

UNDER THE CHARGE OF

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Methods for Administering Fluids.—In the last issue we reviewed briefly the fluid and salt requirements of surgical patients. The next step is to determine the methods by which the materials required may

be supplied. This is especially true in those patients in which the fluid and salt loss is great. There can be no doubt but that the oral method is by far the best if there is not contraindication to the administration of fluids by mouth. With the aid of a Jutte tube large amounts of fluid containing salts and nutritive material can be administered. Unfortunately in the abdominal cases of an obstructive or suppurative character the oral method cannot be used. The subcutaneous method is useful, but even when used as suggested by BARTLETT (*Ann. Surg.*, 1921, 73, 161) with the addition of novocain to the solution it is painful. It cannot, as a rule, be used over a period of many days and free movements of the patient are definitely restricted. The rectal or colonic method has the disadvantage that over long periods the rectum is apt to become intolerant. Furthermore, when large amounts of fluid are necessary this method is not adequate in itself. FLEMING (*J. Am. Med. Assn.*, 1931, 97, 6) has shown that large amounts of fluid in the colon may initiate the spread of an abdominal infection by stimulating peristalsis, a condition which we seek above all to avoid in abdominal suppuration. Increasing evidence published during the past 2 years indicates that little, if any, glucose is absorbed from the rectum or colon. Indeed, McNEALLY and WILLEMS (*Surg., Gynec. and Obst.*, 1929, 49, 794; *Arch. Surg.*, 1931, 22, 649) found that when glucose was added to the fluid placed in the colon the absorption of water was retarded. The work of the above authors and that of PRESSMAN (*AM. J. MED. SCI.*, 1930, 179, 520), EBELING (*Ibid.*, 1932, 183, 876) and SCOTT and ZWEIGHAFT (*Arch. Int. Med.*, 1932, 49, 221) are in agreement that little, if any, glucose is absorbed by this route. Certain of these studies were made in man while others were made in experimental animals. EBELING (*AM. J. MED. SCI.*, 1932, 183, 876) found that only in the markedly hypoglycemic animal did the absorption of glucose from the colon approach that from the ileum. PERUSSE (*Surg., Gynec. and Obst.*, 1932, 54, 770), on the other hand, found that a 1 per cent solution of glucose was absorbed to a greater degree than was a 5 per cent solution. However, the total amount absorbed even when the 1 per cent concentration is used is so small as to be of very little therapeutic value. Most of those who have studied the subject agree that tap water and normal saline are rapidly absorbed from the rectum and colon. The intravenous method has the advantage of permitting fluid to be placed directly in the blood stream. The fluid may be introduced at a predetermined rate so that the amount of fluid, salt and glucose introduced can be accurately estimated. The paper of MATAS (*Ann. Surg.*, 1924, 79, 643) is still one of the classics on this subject. The most distressing aftermath of intravenous infusions is the frequency with which chills occur. STOKES and BUSMAN (*J. Am. Med. Assn.*, 1920, 74, 1013) believed that substances in the rubber tubing were responsible for a large number of these. Many other theories have been advanced, but the work of SEIBERT (*Am. J. Physiol.*, 1923, 67, 90; *Arch. f. exp. Path. u. Pharm.*, 1927, 121, 247) has been the most promising. This worker had found that certain river bacteria, the split products of which pass over in the distillate, are responsible for most of the chills encountered. RADEMAKER (*Ann. Surg.*, 1930, 92, 195) has reported a method of distillation of water and preparation of the solutions which has, to a large extent, eliminated the

chills in those institutions which have adopted the method. VINCENT (*J. Pharm. and Exp. Therap.*, 1929, 36, 107) and HIRSCHFELD, HYMAN and WANGER (*Arch. Int. Med.*, 1931, 47, 259) have pointed out the dangers of rapidly introducing a large amount of fluid in the blood stream. The latter authors were able to produce chills, a fall in the blood pressure and an increase in the pulse rate by the rapid introduction of saline solutions intravenously. When the same solutions were given slowly no such untoward effects were encountered. These results indicate the advantages of the slow continuous intravenous drip. MATAS (*Ann. Surg.*, 1924, 79, 643), HENDON (*Med. Arts and Indianapolis Med. J.*, 1931, 34, 491), AUSTIN and RAVDIN (*Trans. Coll. Phys.*, Philadelphia, 1931, 53, 10) and HORSLEY (*Arch. Surg.*, 1931, 22, 86) have written on the advantages of the slow continuous intravenous drip. In each individual patient the clinician must first determine the needs of the patient from the standpoint of total fluid, salt and glucose and then make use of the methods of administration available to accomplish the desired result in the particular patient.

THERAPEUTICS

UNDER THE CHARGE OF

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Studies on the Treatment of Diabetes by Diathermy of the Pancreas.
—It having been shown experimentally that diathermy is capable of increasing the activity of many of the glands of internal secretion, including the pancreas in experimental animals, RAUSCH (*Deutsch. med. Wchnschr.*, 1932, 58, 1244) applied diathermy as a therapeutic measure in 12 patients with diabetes of varying degrees of severity. In every instance the patient was under adequate control both as to his consumption and his utilization of carbohydrate. The author concludes that in mild cases diathermy has the most favorable results. In such cases its systematic application significantly raises sugar tolerance, even permitting the patient to use greater quantities of carbohydrate than the minimum required so that he may carry on efficiently. The increase in pancreatic activity may even permit the patient to go without the use of insulin. In cases of medium severity the therapeutic value of diathermy is less, for sugar tolerance is only moderately increased, the greatest extent being such as to permit the patient to omit up to about 40 units of insulin. In advanced cases the best that can be hoped for from diathermy is a small reduction in the required dose of insulin. The mechanism by which diathermy produces these effects is believed to be that of increase in insulin production as a result of local improve-

ment of circulation in the pancreas with secondary increase in the activity of the islands of Langerhans. The author obtains the best results when an electrode of 60 sq. cm. of area is applied over the pancreas region combined with one of 100 sq. cm. applied to the abdomen. The intensity of current should be raised to a point of maximal heat tolerance and the duration of treatment should be from $\frac{1}{2}$ to 1 hour, preferably the latter in the majority of cases.

Clinical Comparison of Ergotoxin and Ergotamin.—Notwithstanding the great interest in the chemistry and pharmacology of ergot and its various constituents, there remains considerable uncertainty both as to the clinical action of the alkaloids isolated, as well as to the other constituents present in the crude drug. At the request of the Therapeutic Trials Committee of the Medical Research Council of Great Britain, MOIR (*Brit. Med. J.*, 1932, 1, 1022) undertook to study the clinical effects of ergotoxin ethanesulphonate and ergotamin tartrate (gynergen). As these alkaloids are not used during parturition, but in puerperium, a bag was introduced into the uterus usually at the 7th day of the puerperium. The bag was connected with tubing to a mercury manometer, and this, in turn, was fitted with a float by means of which variations of intrauterine pressure were recorded on a drum. A different patient was used for each test. Twenty-five cases were given either ergotoxin or ergotamin. The ergotoxin salt was tested in 0.25 mg. intravenous, 0.25, 0.5 and 1 mg. intramuscular and 1, 2 and 2.5 mg. oral doses. The ergotamin salt was administered in 0.25 and 0.5 mg. intravenous, 0.25, 0.5 and 1 mg. intramuscular and in 1.5, 2 and 3 mg. oral doses. Both alkaloids were found to be very active in stimulating uterine contractions. After the intravenous doses 4 to 10 minutes elapsed before the onset of contraction; after intramuscular injection 15 to 45 minutes were required. The effect of the oral doses was erratic. After the larger doses the contraction came at about 1-minute intervals. The duration of the effect was in excess of 3 hours. The effect of the alkaloids on the cardiovascular system was not studied. No serious side effects were observed. Three patients complained of a feeling of depression and weight in the head, and 1 patient of nausea and headache. It is concluded that the optimal dosage of both ergotoxin and ergotamin was 0.5 mg. intramuscularly. Doubling this dosage produced but slight increase in action. The observations presented show that ergotamin and ergotoxin are indistinguishable from each other in their clinical actions.

Comparative Studies on Adrenalin, Sympatol and Ephedonal.—The existing confusion as to the relative actions of these three somewhat similarly acting substances upon the pulse, blood pressure and blood sugar lead E. SCHILLING and GERTA KOPP (*Deutsch. med. Wchnschr.*, 1932, 58, 1399) to present the results of a series of parallel observations carried out upon patients. The intramuscular injection of adrenalin in doses of 0.7 to 1 mg. regularly produces a marked rise of blood pressure, blood sugar and pulse rate which persists on the average for more than 2 hours. The similar administration of sympatol in doses of 180 to 240 mg., on the other hand, causes only a very mild and brief rise in blood pressure and blood sugar without detectable influence upon

the pulse rate. Doses of from 1 to 2 grams of sympatol administered orally are without demonstrable effect. Ephetonal given in quantities of 100 mg. orally manifests slight adrenalin-like actions on blood pressure, blood sugar and pulse, but the reactions from such doses are weaker than those which follow the intramuscular injection of 1 mg. of adrenalin.

The Experimental Basis for the Treatment of Bronchitis With Ether According to Bier.—The pharmacologist, T. GORDONOFF, (*Deutsch. med. Wchnschr.*, 1932, 58, 1358) presents the results of his own experiments as well as those of others, in support of the validity of Bier's recommendation of the use of ether in the treatment of bronchitis, particularly the postanesthetic variety. The dose recommended by Bier is 0.5 cc. of ether administered frequently by hypodermic injection. Ether thus employed should be classed as a true expectorant. In the course of its excretion through the lungs it increases respiration, dilates the lung capillaries, produces a slight rise in blood pressure and causes increased blood flow through the lungs. It also increases both the quantity and fluidity of bronchial secretion and apparently in many cases actually enhances the rate at which bronchial secretion is transported out of the lungs by way of the trachea. Combined with the foregoing actions ether exerts an insignificant bactericidal and a more marked bacteriostatic action and probably somewhat facilitates phagocytosis. The author concludes that from an experimental basis ether merits the rank of being peculiarly effective expectorant.

PEDIATRICS

UNDER THE CHARGE OF

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Juvenile Acrodynia: Report of 11 Cases.—CRAWFORD (*Arch. Derm. and Syphilol.*, 1932, 26, 238) states that infantile or juvenile acrodynia is a striking disease syndrome of the neuromuscular and mucocutaneous systems. It has been recognized in Australia for the past 40 years, but only for the past 15 years in the United States and for the past 12 years in Canada. The first cases in England, where it is often called Swift's disease, were those reported by Doak. In continental Europe it was first reported by Feer of Zürich in 1923, and it is often called Feer's disease. It affects infants and children from 2 months to 2 years of age, and occasionally older children and adults. The ages of the majority of the children affected are between 1 and 2 years. Males and females are affected equally. Although all of the cases of this report were white children, some suspected cases have been seen in negro children. The disease lasts from 6 weeks to 1 year. Relapses after a few weeks or months of recovery are frequent. The mortality rate ranges between 5 and 10 per cent. The prognosis should always be guarded as sudden and unexpected deaths occur. The victims are highly susceptible to

pneumonia, which often terminates fatally. In this series the mortality rate was 36 per cent and was due chiefly to pneumonia. The treatment is difficult as there is no specific remedy and symptomatic treatment is of little avail. Sedative drugs are of no value. Feeding is of the greatest importance, as those receiving regular nourishing food usually do well, while those whose diets are inadequate or who refuse food do poorly. Gavage must be used if necessary. Foods rich in vitamins A and B are indicated, and abundant orange and tomato juice, yeast and cod-liver oil seem to be beneficial. A diet of liver has been advocated on the basis that it contains a definite curative factor. Ultra-violet irradiation is of no value. Cold applications to the skin give the most relief. Calamine lotion made up in camphor water is soothing to the general cutaneous surface. Cold wet dressings of 1 per cent boric acid solution, physiologic salt solution, Ringer's solution or very dilute solutions of aluminum acetate to the extremities and the genitalia are soothing. Daily application of olive oil or ointment of rose water tend to keep the skin soft and to prevent dryness.

The Leukocytic Response to Measles.—BENJAMIN and WARD (*Am. J. Dis. Child.*, 1932, 44, 921) studied the leukocytic reactions in 46 cases of measles, including observations on 20 cases during the period of incubation. They used the supravital technique and the analysis was based on the use of a table of normal values for each of the white cell elements during the different ages of childhood. During the incubation period the variations in the numbers of leukocytes was relatively slight. On the first day of the prodromal stage the leukocytic picture showed striking alteration, manifested principally by a fall in the number of lymphocytes. At the height of disease all of the cell elements contribute in the production of a leukopenia. Histologic changes observed in the lymph nodes obtained from one of the patients indicated that the development of the lymphopenia in measles was coincident with marked hyperplasia of the lymphoid tissues. The young leukocytes in the glands did not appear in great numbers in the blood stream until the beginning of convalescence. The onset of the prodromal period of measles is peculiar in that there is usually a fever of quite marked degree with little other evidence of illness. At the same time the blood picture undergoes a marked change that is quite out of proportion to the clinically mild appearance of the illness. This is a point very highly suggestive of measles.

Antitoxin Content of the Blood Serum of Children With Negative Reactions to the Schick Test.—MESSELOFF and KARSH (*Am. J. Dis. Child.*, 1932, 44, 999) titrated the blood of 51 children with negative Schick reactions for the antitoxin content. Forty-eight (94 per cent) had at least $\frac{1}{30}$ unit of antitoxin per cubic centimeter of blood serum. In 1 case this value was between $\frac{1}{30}$ and $\frac{1}{100}$ unit, and in 2 other cases between $\frac{1}{30}$ and $\frac{1}{5}$ unit per cubic centimeter of serum. They did not find any child with a negative reaction to the Schick test with no antitoxin in the blood. In cases reported with negative Schick reactions with little or no antitoxin in the blood, this discrepancy has in all probability resulted from the use of a toxin of questionable potency in making

the test. A standardized, potent toxin is essential for obtaining consistently correct results. In certain individuals a reaction to the Schick test will be positive in from 24 to 48 hours, but will become negative after that time. This type of reaction is found in those having less than the usual $\frac{1}{30}$ unit of antitoxin per cubic centimeter of serum. From the standpoint of immunity against diphtheria such individuals present no great problem, as they possess usually sufficient immunity to protect them against the development of diphtheria. As a rule the Schick test when correctly performed with an efficient material is a practical and reliable indicator of the presence of diphtheria antitoxin in the blood in an amount sufficient to protect the individual against clinical diphtheria.

The Prevention of Rickets.—MITCHELL and COLEY (*J. Am. Med. Assn.*, 1932, 99, 1768) began their study with a group of 250 babies, but by the time their second birthdays had been reached, the group had been narrowed down to 139 who had continued under observation. Of these, 31 (22.3 per cent) at some time during the study showed clinical evidence of rickets. In a control group the total incidence of rickets in the first 2 years of life was 54.2 per cent. On at least 1 Roentgen examination the condition in 22 (15.9 per cent) was diagnosed as rachitic. The difference between the number of positive findings on clinical and on Roentgen examination compared favorably with the observations as reported by others. Two reasons are given as an explanation of the high incidence in this series as compared with that given by other observers. This first is that these cases were studied over a longer period as compared to a few months in other series. The second is that the second year is considered and as was shown in an earlier report the highest percentage of positive results were seen during the second year. In most other reports the observations were begun and ended prior to the end of the first year. An additional factor is the inclusion of all children who at any time showed clinical or Roentgen evidence of rickets. Either cod-liver oil, in doses of 2 or 3 teaspoonfuls daily, or viosterol, in doses of 8 to 10 drops daily, exerts a definite influence against the development of rickets, and by either treatment severe or even moderately marked rickets may be prevented in babies who live under good conditions of hygiene. In spite of this treatment, 22.3 per cent of patients showed clinically mild rickets. In 51.9 per cent of the cases Roentgen findings were positive. The administration of cod-liver oil as mentioned before protected 82 per cent of the patients, while the dose of viosterol mentioned completely protects only 75 per cent, in spite of the fact that the amount of viosterol has a little more than twice the amount of vitamin D contained in the daily dose of cod-liver oil. The lowest prevalence of rickets, 9.9 per cent, occurred among those given sunbaths in summer and viosterol and cod-liver oil in winter. The ultraviolet irradiation proved a satisfactory substitute for the sunbaths. In the causation of rickets there must be other factors than a deficiency of vitamin D such as a comparative deficiency of vitamin A, a deficiency of minerals in the diet, or perhaps some other as yet unrecognized agent in which the influence of light plays as important a part as it does in the activation of ergosterol.

DERMATOLOGY AND SYPHILIS

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Lymphogranulomatosis Inguinale, or Durand-Nicolas-Favre Disease.—An increasing amount of attention has been focused on this so-called fourth venereal disease in the past few years, and ZAKON (*Arch. Dermat. and Syph.*, 1932, 26, 238) gives an excellent review of its literature, outlines the clinical features and reports 3 additional cases. Lymphogranulomatosis inguinale is a subacute indolent inguinal adenitis of venereal origin which begins as a solitary nodular, papular or herpetiform lesion on the surface of the prepuce or in the coronary sulcus. An intraurethral erosion may initiate the process. The initial lesion is characterized by its small size, nonpainful character and its evanescence, and is followed within an average period of from 2 to 3 weeks by a progressive inguinal adenitis and mild constitutional symptoms. The glands become more and more adherent to the skin, which breaks down to produce sinuses exuding primarily a small amount of sticky pus which becomes more abundant as secondary infection occurs. The etiologic factor is undetermined. A specific diagnostic test for lymphogranulomatosis inguinale was introduced by Frei in 1925. The antigen is prepared from pus obtained by puncture of the buboes. The material is diluted 5 to 10 times with physiologic salt solution, heated at 60° C. for 2 hours on 1 day and for 1 hour the next day, and subjected to the usual tests for sterility. One-tenth cubic centimeter of this antigen is injected intracutaneously, a positive test consisting of a reddish, infiltrated papule which appears within 48 hours. A positive reaction may be delayed for 8 or 10 weeks after the onset of the affection but can be obtained months or even years after the appearance of the adenitis.

Erythema Nodosum.—An organism of the genus *Corynebacterium* has been cultivated from the subcutaneous tissue in each of 3 cases of erythema nodosum by MOON and STAUSS (*Arch. Dermat. and Syph.*, 1932, 26, 78). In a case of unusual severity the organism was also cultivated from the blood stream. In 13 of 14 inoculated animals lesions were produced that had the histologic appearance of erythema nodosum, and the same organism was recovered in cultures from these lesions. The authors believe that the organism found in the reported cases is identical with that described by Rosenow and suggest that it be designated *Corynebacterium cutis-nodosæ*.

GYNECOLOGY AND OBSTETRICS

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Histogenesis of Papillary Ovarian Cysts.—The exact origin of papillary cysts of the ovary has never been definitely determined, although many theories have been advanced. This subject has been investigated histologically at The Mayo Clinic by McCARTY (*Surg., Gynec. and Obst.*, 1932, 54, 188), who found small, cortical, epithelial structures of a cystic nature in 100 per cent of the grossly normal ovaries which were removed with papillary ovarian cysts of the opposite side, whereas in the normal control group the structures were found in only 64 per cent of the cases. These structures are of germinal epithelial origin. The superficial papillomata were found about twice as frequently in grossly normal ovaries which had been removed with intracystic papillary ovarian cysts of the opposite ovary, as in the ovaries from normal controls. From the microscopic appearance it would seem that these structures are closely related to the papillary ovarian cysts. In this series of cases very little evidence was obtained to indicate that the Graafian follicles or the rete of the ovary are frequent sources of origin of the papillary ovarian cyst. Therefore, he believes that it may be stated: (1) That most papillary ovarian cysts probably develop from the small germinal epithelial cystic structures found in the cortex of the normal ovary, and (2) that the grossly normal ovary which is found in association with an intracystic papillary ovarian cyst of the opposite ovary is a potential danger and should always be removed, age permitting. This study reinforces from the laboratory what most operating gynecologists have believed for many years, namely, that in the presence of a papillary cyst of one ovary, it is usually good judgment to remove both ovaries in order to forestall the probable future trouble in the remaining ovary even though apparently healthy at the time.

Postmenopausal Bleeding.—Vaginal bleeding occurring after the menopause should never be disregarded by either the patient or the attending physician until the etiologic factor has been determined. While in the majority of cases the bleeding is caused by some type of carcinoma it is not always due to this cause. In a survey of 98 cases of bleeding of this type which was made by KANTER and KLAUWANS (*Am. J. Obst. and Gynec.*, 1932, 24, 192), the cause was found to be, in order of frequency, carcinoma (67 cases), cervical polyps (8 cases), fibromyomas (7 cases), uterine prolapse (5 cases), senile vaginitis (3 cases), cervical erosion (3 cases), urethral caruncle (2 cases), uterine

fibrosis (2 cases), and nonspecific ulcer of the vagina (1 case). Of the 67 carcinomas in the series, 51 were cervical, 11 were fundal, 2 were on the vulva, 1 was in the vagina and 2 were ovarian. In the series therefore, 68.4 per cent of the cases were of a malignant nature and 31.6 per cent were benign, so that the axiom "all cases of postmenopausal bleeding should be considered as malignant until proved otherwise" is very significant. They emphasize that once the menopause has been definitely established (no menses for a period of from 6 months to a year) all bleeding from the genitals should be considered as abnormal since there is no apparent relationship between the type or amount of bleeding and the seriousness of the existing condition. From their survey they also feel that parity, length of time in the menopause and the duration of active menstrual life are of no particular value as diagnostic aids.

Myoma Operations During Pregnancy.—This subject which is one of frequent discussion has been summarized by MAYER (*Zentralbl. f. Gyn.*, 1932, 56, 1922) of Tübingen by stating that there are three ways of handling this complication: (1) By extreme conservatism, with consideration only for the life of the fetus; (2) consideration only of the patient and having little regard for the continuation of the pregnancy, and (3) taking into consideration the interest of both mother and child as described below. As long as the myoma and the pregnancy give no great amount of trouble, they should be left alone. However, if the tumor gives much pain, so that if pregnancy were not present operation would be indicated, the existence of an associated pregnancy is not an absolute contraindication against operation. If operation be undertaken it should not consist of hysterectomy but rather myomectomy with preservation of the pregnancy. Only rarely does the patient abort after myomectomy but, even if this should occur, at least the uterus is preserved for future pregnancy.

Effect of Knee-chest Position.—In order to determine whether the knee-chest position during the postpartum period accomplishes all that has been claimed for it, SCHAUFFLER (*J. Am. Med. Assn.*, 1932, 99, 726) has made some controlled observations which tend to contradict generally accepted opinions. Following delivery the uterus is normally in a position approximating first-degree retroversion. Theoretically, this tendency is increased through the dorsal posture of the patient in bed, which is more or less routine. The natural tendency of the heavy corpus to drop back against the sacral promontory is thus accentuated. One would naturally suppose that a ventral posture favoring a dropping forward of the heavy corpus would aid the natural forces, but unfortunately the observations in this study constitute a definite and surprising contradiction to this belief. This series of 169 patients were nearly all vigorous young women (about 90 per cent primiparous) and presented a group practically free from complicating factors such as retroversion from previous pregnancy, prolapse and the like. Alternate patients were put on a special regimen consisting of the ventral posture in bed, and the knee-chest position beginning on the 8th day postpartum and increasing to 20 minutes twice a day. On the 18th day they were

started on the camel walk, and instructed to rest as nearly as possible entirely on the abdomen while in the prone position. The other half of the group were given no exercises whatever. The incidence of retroversion following the knee-chest position was 47.2 per cent as opposed to 34.5 per cent for the group which did not assume this position. It may be unfair to conclude that the use of the knee-chest position actually increases the incidence of postpartum retroversion, but Schaufler believes that the confidence that has always been placed in it as a therapeutic measure is no longer justified.

OPHTHALMOLOGY

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Classification of the Optic Atrophies.—PATON (*Proc. Roy. Soc. Med.*, 1930, 24, 25) thinks that atrophies of the optic nerve should be classified into those of localized origin, those of diffuse or indeterminate origin and those of unknown origin. The atrophies of localized origin may be retinal, papillary or retrobulbar. The retrobulbar atrophies may be intraorbital, foraminal or intracranial. In the group of retinal atrophies belong retinitis pigmentosa, amaurotic family idiocy, cerebromacular degeneration, macular without cerebral degeneration and the atrophies secondary to retinal and choroidoretinal inflammations and vascular degenerations. The essential cause of the atrophy of the nerve in these cases is the degeneration of the ganglion cells of the retina. Certain of the toxic amblyopias may belong to this group. To the group of papillary atrophies belong glaucoma, cavernous degeneration in high myopia, atrophy secondary to papillitis and papilledema and traumatic avulsion of the optic nerve. As a result of long-standing edema of the disk, the nerve fibers swell, undergo fatty degeneration and are replaced by neuroglial proliferation which in its contraction squeezes out the remaining intact nerve fibers. Added to this is the obliteration of the smaller vessel channels by endothelial proliferation. An atrophy of the intraorbital retrobulbar type is the result of an inflammation affecting the parenchyma of the nerve directly or extending inward from the meninges. The commonest cause of parenchymatous inflammation is disseminated sclerosis, but postinfluenzal, syphilitic, postherpetic and other types of myelitis can occur. The interstitial or meningitic type of atrophy may result from septic, tuberculous or syphilitic meningitis, or from orbital inflammations secondary to sinus infections or dental abscesses. Intraneural or extraneural tumors in the orbit can also cause retrobulbar atrophy. The foraminal type

of retrobulbar atrophy is most commonly seen in head injuries, the trauma not necessarily involving the foramen directly in a fracture but resulting in nerve tears and hemorrhages into the nerve sheaths. It occurs also in Paget's disease, in leontiasis ossea and in osteitis deformans. The field changes in these cases are very irregular, peripheral contractions, ring scotomata and paracentral scotomata. Sclerotic changes in the ophthalmic artery as it passes through the foramen may cause a similar type of atrophy. The intracranial type of retrobulbar atrophy is most often due to tumors in the pituitary or suprapituitary regions, on the base of the frontal lobe, or at the anterior end of the temporosphenoidal lobe. Disseminated sclerosis and meningitis also may cause this type of atrophy, as well as basal aneurysms, and sclerotic changes in the internal carotid. The site of the primary affection of the optic nerve is not definitely known in the atrophies due to general toxins such as tobacco, methyl alcohol, carbon bisulphid, diabetes and the anemias. It may be in the ganglion cells of the retina or in the nerve fibers behind the globe. Quinin and aspidium filix-mas produce retinal arterial spasm and secondary retinal atrophy. Arsenic apparently affects the nerve fibers directly. Lead acts on the nerve fibers directly or indirectly through arterial degenerations. Among the atrophies of unknown origin must be placed Leber's familial atrophy and the atrophies associated with degenerations of the central nervous system, such as Friedreich's disease, peroneal atrophy and hereditary cerebellar atrophy. Tabetic atrophy is partly interstitial and partly parenchymatous in type. Either element may predominate in a given case, with corresponding differences in the course of the atrophy. Thus the onset may be gradual with segmental losses in the peripheral fields, but with fair preservation of central visual acuity over a long period; or rather rapid loss of central visual acuity and of color fields may occur while the peripheral fields for white are well preserved. The atrophic process commences, as a general rule, in the proximal and not in the distal or peripheral portion of the optic nerve.

Pathogenesis of Retinitis Pigmentosa.—For the study of pigmentary degeneration of the retina in its relationship to the local pathogenesis of retinitis pigmentosa, FRIEDENWALD and CHAN (*Arch. Ophth.*, 1932, 8, 173) injected suspensions of washed melanin granules obtained from the retinal pigment epithelium of cows' and pigs' eyes into the vitreous of albino rabbits. Clinically, after several weeks, some of the pigment was seen to have entered the retina, at first in the periphery, and later near the optic disk where it usually arranged itself around the blood-vessels as in retinitis pigmentosa. Histologically, in eyes enucleated 4 to 6 months after the injection monocyctic phagocytes containing pigment were found in the vitreous and on the surface of and in the retina. Müller's cells and fibers were also found to be packed with pigment. In eyes enucleated at longer periods after injection Müller's fibers were found to be markedly proliferated and the retinal tissues were found to be markedly disorganized in the regions where the phagocytosis of pigment was most active. The damage was greatest in the ganglion cells, and next in the neuroepithelium. In regions in which pigment was present in the retina but had not been phagocytosed the retinal

cells were not damaged. It seemed, therefore, that the destruction of the retinal cells was due to the passage of active phagocytes through the retina for the removal of the pigment granules. It seems probable that in retinitis pigmentosa there is a continuous discharge of pigment into the retina and that the resultant phagocytic invasion of the retina produces the destruction of the retinal elements, the overgrowth of Müller's fibers, and the secondary atrophy of the optic nerves. Whether the primary lesion lies in the pigment epithelium itself or in the neuro-epithelium is still a matter of conjecture.

RADIOLOGY

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Encephalography in Children.—ELEY and VOGT (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 686) regard encephalography as a valuable diagnostic procedure in the study of fixed lesions of the brain in children. Its principal contraindication is increased intracranial pressure as evidenced by papilledema, etc. Although the encephalogram gives a definite impression of the gross pathologic condition, it will not determine the cause of the pathologic changes. Trauma, hemorrhage, developmental defects and infections all produce pathologic changes which ultimately are similar in the encephalogram. Little is known concerning the size of the subarachnoid space in normal infants and children, and though certain normal standards are accepted, there are frequent occasions when the maskings are equivocal. The authors believe that probably one of the most important uses of encephalography will be its employment in the selection of cases of epilepsy suitable for treatment.

The Roentgen Findings in Chronic Progressive Bulbar Palsy.—The earliest symptom of bulbar palsy is difficulty in swallowing and this is likely to bring the patient to the roentgenologist. CHRISTIE (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 717) has recently observed an instance in a man, aged 27 years, who for 2 years had had difficulty in swallowing. It was possible with complete extension of the head to swallow small quantities of water, but large quantities could not pass and produced choking. The Roentgen examination showed a delay in swallowing taking place entirely in the pharynx. Fluid was almost immediately regurgitated and some of it entered the larynx causing the patient to cough. Only a very small amount passed into the esophagus. There was no evidence of a foreign body or of any lesion reducing the lumen of the pharynx or esophagus, and the lungs, pleura

and mediastinum were negative. On neurologic examination a diagnosis of bulbar palsy was made. Among early symptoms which may be suggestive to the roentgenologist are slight blurring of speech, inability to pucker the lips and a nasal voice.

Agranulocytic Angina.—Agranulocytosis, a term used to designate a condition in which the granular elements of the blood are lacking, was first described by Schultz, in 1922. This blood dyscrasia is usually an accompaniment of severe throat lesions, and Friedemann suggested the designation of angina agranulocytica. The disease occurs chiefly in middle-aged women, and prior to the employment of Roentgen therapy the mortality was as high as 91 per cent. By irradiation in small doses in conjunction with blood transfusion and other measures the mortality has been lowered. WATERS and FIROR (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 740) treated 5 cases with small doses directed to the marrow of the long bones. Three patients recovered, and this experience together with the results of animal experimentation conducted by the authors seems to warrant further employment of the method.

A Roentgenographic Study of Glass and Its Visibility as a Foreign Body.—LEWIS (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 853) has investigated the very practical question of whether glass particles embedded in the body can be revealed with Roentgen rays. Grouped according to their permeability by the rays, glass is of two classes: (1) ordinary and (2) lead and barium glass. Lead and barium glass are used occasionally for lenses, crystal table ware, art ware, tubing, thermometers and electric light bulbs. A particle of lead or barium glass, even smaller than 2 mm. in diameter, lodged anywhere in the soft tissues of the body, might be expected to be shown by thorough roentgenographic study. Most of the glass which might be encountered as a foreign body, such as window glass, automobile glass, fragments of bottles or clinical thermometers, etc., belongs in the ordinary group. Nevertheless a particle of ordinary glass might be expected to be shown clearly in the soft tissues of the upper extremity or leg, and under favorable conditions in the thigh, abdomen or pelvis.

The Roentgen Signs of Tuberculosis of the Vertebral Body.—One hundred cases of tuberculosis of the spine were studied by DAUB and BADGLEY (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 827). The average age of the patients was 29 years and the average duration of symptoms at the time of examination was $6\frac{1}{2}$ years. Roentgenologically the following types are to be distinguished: (1) Central, (2) intervertebral articular and (3) anterior. The central type is more common in the dorsal area, and the intervertebral in the lumbar segment. The central variety causes collapse of the vertebral body in a high percentage of cases, while the body is preserved until late in the disease in the intervertebral type. Narrowing of the disk is the earliest and most constant sign in tuberculosis of the spine. Abscess is the most common complication and was found in 84 per cent of this series. Skipped infection, or 2 foci of infection with normal vertebrae between, was found in 10 per cent of the cases. Concomitant tuberculosis in other parts of the body was present in 53 instances; pulmonary lesions were most common and occurred in 24 cases.

NEUROLOGY AND PSYCHIATRY

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Psychological Factors in the Prevention and Treatment of Alcohol and Drug Addiction.—REES (*Lancet*, 1932, 2, 929) states that alcoholism and drug addiction are in almost every case the symptoms of a psychologic maladjustment; a relief from a sense of oppression at having to stand up to the circumstances of life. This habit is usually developed from the spoiled and indulged child who meets difficulty when he comes into the world as an adult, those with an inferiority complex resulting from a previous sense of superiority, the self-conscious, who can by it gain courage; forgetfulness, and put themselves more in tune with life. The aim of the treatment should be the discovery of the cause of the maladjustment so that the patient can be gotten to see and realize his own problem. Methods of psychotherapeutic approach are persuasion, suggestion and mental analysis, necessitating a doctor with a great deal of insight and a great interest in the personality of his patient. Increased knowledge on the part of the doctors as to the ways in which neurotic tendencies arise in the individual will help in the future in producing a better-balanced and adjusted race, not requiring the wrong use of drugs. Much is being done by emphasizing the advantages of right living and thinking, and by inculcating the courage and the spirit of adventure, which is better than emphasizing warnings and prohibitions. Parental education is being undertaken which means wiser and more understanding treatment of the child in the early years.

Suicide: Social, Forensic and Psychological Aspects.—MAJOR C. R. BELL (*Milit. Surg.*, 1932, 71, 399). *Sociologic aspects:* SIR HUBERT BOND reports no history of suicide before the 18th century, omitting Biblical, classical and medieval references. The average number of successful suicides in England and Wales each year is about 5000; of these only about 50 occur in the certified insane. There is an increase in the number of attempted suicides reported, which is short of the real total. During the census years, 1901, 1911, 1921, the suicide rate per 10,000 population was 1 for both sexes and for 1929, 1.3 for both sexes. Sir Hubert gives proportions of suicides as to sex and the means of suicide as to sex. Women have a higher percentage with jumping from high places, drowning, poisoning; men, use of cutting or piercing instruments, hanging or strangulation, crushing and use of firearms. Since 1921 an increase in the use of coal gas by inhalation has occurred, due largely to the nature of its action and its ready availability. *The forensic aspect:* W. N. EAST asserts that suicide

connotes to the legalist a crime and to the physician a state of emotional disorder. It was originally an ecclesiastical offense. The ancient custom was to bury a suicide at a crossroads with a stake driven through his body, and in the early 13th century a person who committed suicide in order to avoid conviction for a crime forfeited his lands. Suicide in English law is a felony—self-murder, and the recovered offender may be committed for trial and punished by imprisonment with hard labor. An analysis of 1000 consecutive cases of attempted suicide showed only about one-fifth were certifiable insane, but many suffered from temporary mental disorder. These are detained indefinitely for observation and treatment. *Psychologic aspect:* H. CRICHTON-MILLER believes that the majority of suicides are not acts of the insane, but man's retreat from life and reality. Underlying motives are: (1) Physical pain, or anticipated pain or insanity, and frustration of instinctive demands, especially of the sex instinct. (2) Social sufferings and fears—the bankrupts, those out of employment, or facing exposure of misdeeds, remorse for wrongs committed, illegitimate pregnancy, those with an "inherited tendency" for suicide. (3) Doubts and fears of the hereafter. In some social systems self-destruction under certain circumstances is regarded as a virtuous act. Other cases are self-punishment, the supreme sacrifice for some redemptive purpose, melancholics and cyclathymics. The majority of people committing suicide are not the insane but the "borderline insane," the "deviate" and the "psychopathic."

PATHOLOGY AND BACTERIOLOGY

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The Stem Cell of the Monocyte.—RINEHART (*Arch. Path.*, 1932, 6, 889) made use of a previously described (*Anat. Rec.*, 1932, 52, 151) method of silver impregnation of blood films in attempting to trace the nuclear development of the monocyte from its parent cell. Studies reported were carried on with blood obtained from a human case of monocytic leukemia, studied during a period of 18 days, from hospital admission until death. Mature monocytes ranged from 72 to 96 per cent, young monocytes from 2 to 20 per cent, and monoblasts from 1 to 5 per cent; the total white count running between 34,000 and 150,000. A small number of cells were observed, corresponding in nuclear architecture to the hemohistioblast of Ferrata. Many, with nuclear structure intermediate in form between the hemohistioblast and monocyte were noted. In a single blood film, cells representing all gradations in the transformation from hemohistioblast to mature monocyte were

present. The results are in accord with those of Ferrata and coworkers, and further, favor the view held by Cunningham, Sabin and Doan, "that the precursor of the monocyte is an undifferentiated mesenchymal cell."

Experimental Production of Sidero-fibrotic Lesions in the Spleen.—FASIANI and OSELLADORE (*Virch. Arch. f. path. Anat.*, 1932, 284, 474) report an experimental study of that peculiar lesion of the human spleen which has been variously referred to as mycosis, calcium-iron incrustation, siderofibrosis, and Gandy's or Gandy-gamma nodules. To the naked eye the lesions appear as tobacco-colored cicatricial flecks on the cut surface of the spleen, usually with a depressed puckering of the overlying capsule. Microscopically the lesion is seen to be within a trabeculum in close relationship to the larger bloodvessels and is characterized by a tangled fibrous core with a hemorrhagic zone around the periphery. The central part contains (1) peculiar fibrillar or rodlike structures, not infrequently segmented like mycelia; some of these are deeply basophilic, others remain pale; (2) tiny basophilic spherules, somewhat like spore forms of a yeast organism, sometimes concentrically laminated; (3) occasional foreign-body giant cells. In the rodlike formations and spherules, iron and calcium in varying proportions are demonstrable by special stains. These structures, because of their resemblance to fungoid organisms were thought by some authors to represent a parasitic cause of the lesion but the authors of this article regard the parasitic theory as disproven. They succeeded in reproducing the lesion in dogs by first producing congestion through partial ligation of the splenic vessels, and then traumatizing certain areas of the spleen with electrocautery or injections of calcium chlorid. It was noteworthy that while the experiment succeeded with dogs, rabbits and cats gave negative results though treated in exactly the same manner. The authors regard the lesion as one which results from circumscribed degenerative or necrotic foci occurring in a spleen through which the blood flow is impeded. They look upon the mycelia-like forms and the round bodies as inert products of degeneration formed of tissue remnants. Now that a means has been devised of producing the lesion experimentally the way is opened for investigation of the causation of the lesion in the human spleen.

Marrow Hyperplasia and Hemoglobin Reserve in Experimental Anemia Due to Bleeding.—OEHLBECK, ROBSCHT-ROBBINS and WHIPPLE (*J. Exp. Med.*, 1932, 56, 425) detail the results obtained and conclusions drawn from observations conducted upon 18 dogs whose blood hemoglobin level was kept at 40 to 50 per cent by repeated blood-letting (instead of the normal 140 to 150 per cent) for varying periods: from 1 year and 4 months to 7 years and 4 months. As the dogs died, of anesthesia, natural causes, or accident, they were autopsied, and all vertebræ, ribs and long bones split and examined. In but 2 was there evidence of marrow exhaustion. Many showed red marrow spread, but strangely there was no relation between the amount of hemoglobin produced in life and the degree of marrow spread encountered post-

mortem. Changes in other organs included those of senility for the most part. The splenic pulp showed erythrogenesis, but to a small degree. There was no evidence of marrow metaplasia in the livers. In dogs possessing a theoretical hemoglobin reserve, its existence in the form of red cells in the marrow was not evident. Three of the dogs, that had been splenectomized, presented no change in morphologic manifestations or course of the anemia. It was notable that all of the dogs remained in remarkable health despite the prolonged, oft-repeated loss of blood.

The Etiology of Colds.—The common cold has long been recognized as not only the cause of great discomfort and loss of time but as the preliminary stage of many of the more serious diseases of the respiratory tract. It has been found extremely difficult to arrive at any logical conception applicable to even the majority of cases as to the etiologic agent or agents which might be held responsible for the variety of manifestations. WALKER (*Ann. Int. Med.*, 1932, 5, 1526) has shown that the reported experiments relating to the hypothesis that colds are due to a filtrable virus are inadequate to support the hypothesis, and because of the numerous disturbing factors, each difficult to control, he doubts whether the hypothesis can be submitted to proper experimental test. He further brings evidence to support the view that bacteria are the extrinsic factors in the etiology suggesting that the reaction may be very similar to that in hay fever but in addition the etiologic agents possess the power of multiplication and of tissue invasion—merely the late appearance of an organism in cultures being insufficient to displace it from the position of primary etiology. HILDING (*Ann. Int. Med.*, 1932, 6, 227) has studied the problem from the physiologic aspect and described four defenses of the upper respiratory tract: ciliary action, exchange of mucin, regeneration and adaptability. The epithelium he showed to be dynamic and intensely active, the cilia moving tremendous loads of mucin and foreign material, the layer of mucin—resembling another lining membrane—is frequently changed being moved rapidly over the ciliated areas and more slowly under traction in the non-ciliated regions. Bacteria are removed rapidly in the deeper parts of the nose and this may explain, he believed, the fact of cultures from these parts being so often sterile, the regions where they do lodge in large numbers however, drain very largely through the meatuses, where cultures are not usually taken. He found that the mucosa, when an irritant attacks from the surface, readily sloughs its injured cells before they are dead and replaces them rapidly by prolific regeneration, which he considered as part of the physiologic process. Further, his experiments indicated that the epithelium can radically and rapidly alter its form according to demands made upon it and that the different types of epithelium are merely various forms of the same general respiratory epithelium. It seems obvious to the Reviewer from the above studies, and the experience of clinicians and laboratory workers, that the search for a specific agent of widespread applicability as the fundamental etiologic cause of colds is extremely complicated and it is not easy to even formulate the necessary qualities of such an agent, if such there be.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Purification of the Virus of Vaccinia.—BEHRENS and MORGAN (*J. Infect. Dis.*, 1932, 50, 277) found that much more acid had to be added to the dermovirus emulsion than to the neurovirus emulsion used in their experiments, in order to coagulate the cellular and scab material, and this probably affected the virus. Less virus would, however, theoretically, be freed in the case of the dermovirus emulsion, because the isoelectric points of the two components are closer together. The isoelectric method of purification is satisfactory for the neurovirus emulsion, but not for the dermovirus. It does, however, serve the purpose of confirming the assumption that the virus obeys colloidal chemical laws. Both the isoelectric and the aluminum gel methods, which were developed by the authors for the purification of the virus of vaccinia, are satisfactory for neurovirus emulsions.

Prevalence of Venereal Disease in New Orleans, La.—CLARK and USILTON (*Pub. Health Rep.*, 1932, 47, 1187) report that venereal disease prevalence surveys have been made in a number of American cities. The figures run as high as 20 per thousand population for Memphis, Tenn., to as low as 6.8 for New Orleans. The following is the summary of the data on New Orleans: In New Orleans a 1-day census showed that 32 per cent of the physicians had one or more cases of venereal disease under treatment. There was practically an even distribution of cases reported in private practice and in public clinics or other institutions. There were reported 4820 cases of syphilis and gonorrhea under treatment as of the survey date, February 2, 1931, of which 2676 were syphilis and 2144 gonorrhea. The rate was nearly twice as high among the colored population as among the white. The gonorrhea rate for colored females was found to be extremely low. The investigators have no reason to offer for this finding. There are 90 per cent of the private practice cases in the hands of 15 per cent of the physicians. It is thought, perhaps, that the adequate public clinic facilities for treatment of syphilis and gonorrhea are responsible for the fact that there is so much specialization in these diseases among the private practitioners. Although the concentration of these cases in the care of a few physicians greatly assists in the dissemination of the treatment data on venereal diseases, it is felt that here as in other communities many, if not most, of the early infections are seen first by the family physician, and he should be trained in the early recognition, if not specially in the treat-

ment, of these diseases. The ratio of incidence to prevalence of syphilis is nearly twice as high for the males as for the females, whereas for gonorrhea it is quite similar for the two sexes.

New Orleans was found to have a lower venereal disease prevalence rate than any of the other 10 large cities in which a survey was conducted. However, in conjunction with the prevalence survey in New Orleans a study of the amount of treatment given by unauthorized medical sources was found to be very high. It also was found that at least one-half of the whites and 80 per cent of the colored attempted either self-treatment or were treated over the drug store counter before applying to a clinic for treatment. For these reasons there is a question as to whether the apparently low prevalence rate in New Orleans is due entirely to the effectiveness of the control methods and the excellent free public clinic facilities or to other reasons. The authors do feel, however, that very complete returns were made from those coöperating in the study.

Diphtheria Antibodies Transmitted to the Offspring of Immune Guinea Pigs.—RICHARDSON (*J. Immunol.*, 1932, 22, 351) made measurements of the diphtheria antibodies, antibacterial and antitoxic, in the sera of the offspring of guinea pigs previously immunized with diphtheria filtrate. The data showed that diphtheria antibodies of the antibacterial sort as well as antitoxin are placentally transmitted. The proportion of $\frac{\text{antitoxin antibodies}}{\text{nonantitoxin antibodies}}$ found in the sera of the offspring shortly after birth was comparable to that in the sera of their respective mothers. The sera of a number of families were studied over periods of 60 or more days following the births; the data of these tests showed that the amount of antibodies originally transferred by the mother is the important factor in determining the duration of the passive immunity of the offspring.

An Epidemic of Croupous Pneumonia Caused by Pneumococcus Type I.—STROM (*J. Infect. Dis.*, 1932, 50, 430) describes an epidemic of lobar croupous pneumonia in an orphanage caused by pneumococcus Type I. Pneumococcus Type I was found in the sputums and in cultures from the nose and throats of the patients during illness and up to 73 days after the crisis. In one case, it was found in a culture from the nose and throat 4 days before the onset of the disease. Of the contacts 33.3 per cent were found to be carriers during the height of the epidemic, and 16.9 per cent, $2\frac{1}{2}$ months later. The strains from the patients were more virulent in mice than those from the carriers. The disease was more prevalent among the older boys than among the younger ones, presumably because the former represented a more rural population than the latter.

Food Poisoning Due to Toxic Substances Formed by Strains of the Cloacæ-Aërogenes Group.—GILBERT, COLEMAN and LAVIANO (*Am. J. Pub. Health*, 1932, 22, 721) report an outbreak of at least 125 cases of food poisoning extending over 2 successive days in October, 1930. The epidemiologic findings indicated that cream puffs and chocolate eclairs

manufactured by a wholesale bakery had been eaten by all those who became ill. Symptoms, including prolonged vomiting, profuse diarrhea and cramps, but without rise of temperature, developed within 2 or 3 hours after ingestion of the food and generally subsided in from 4 to 10 hours. Cases occurring on the second day were more severe than those of the first day. A strain of bacilli belonging to the cloacæ-aërogenes group was isolated from samples of the pastry filling as well as from fecal specimens from 5 patients. Filtrates of a medium containing ingredients corresponding to those in the cream filling, in which this organism had been grown for 48 hours, were toxic for rabbits and chickens. The toxic substance from these cultures did not seem to be appreciably altered by heating to the boiling point. Staphylococci and other bacteria isolated were studied similarly, but none of the organisms tested showed evidence of toxicity. The presence of poisonous chemicals could not be demonstrated. Examination of the bakery indicated that the food was prepared under cleanly conditions but that the cream filling was left standing at room temperature for several hours before the shells were filled. After being kept in a refrigerator overnight the pastries were distributed over a considerable territory the following day by automobile truck without refrigerating equipment. Thus an opportunity was afforded for bacteria which might have been present to develop and for toxic substances to be produced by them.

Effect of Lead Arsenate Spray on the Composition and Vitamin Content of Oranges.—NELSON and MOTTERN (*Am. J. Pub. Health.*, 1932, 22, 587) present data to show that oranges produced by trees sprayed with lead arsenate differ in chemical composition from normal oranges. The most pronounced difference is a reduction in acidity of the juice; there is also a decrease in sucrose with a corresponding increase in invert sugar. The arsenic content of the edible portion of the orange was not changed by spraying the tree with heavy doses of lead arsenate. The authors conclude from the experiments that have been completed that the vitamin C content of heavily sprayed oranges is decreased fully one-third and it may be only one-half of that of unsprayed fruit.

Tularemia: Occurrence in the Sage Hen.—PARKER, PHILIP and DAVIS (*U. S. Pub. Health Rep.*, 1932, 47, 479) report on tularemia of birds, not only on account of the interest from the point of view of a new natural host of tularemia infection but also because there is a possibility of human infection from birds. Four cases are mentioned in which the infection seems to have been traceable to game birds. The data also indicate that a bird tick is concerned in the maintenance and transfer of tularemia among lower animals.

The Races of *A. Maculipennis*.—HACKETT, MARTINI and MISSIROLI (*Am. J. Hyg.*, 1932, 16, 137) state that explanation of "anophelism without malaria" and of the fact that, in Europe, malaria incidence does not seem to be in satisfactory correlation with the density of *A. maculipennis* has been sought in the existence of races of *maculipennis* with different bionomic characteristics and different potentialities of malaria transmission. Races have been distinguished in France and

in Holland on the basis of average measurements of some structural character, but such a statistical method is not serviceable in identifying individual specimens, or in determining the racial composition of a given maculipennis population. Only pure strains can profitably be compared in this way, and the method gives us no criteria for recognizing a pure strain. On the other hand, by study of the egg markings and structural peculiarities, Falleroni discovered a fundamental division of maculipennis species into two races, and our observations in many areas of Germany and Italy have confirmed and extended this conception. One race (*A. maculipennis labbranchiae* Falleroni) lays a uniformly dappled egg with relatively small floats posteriorly placed. The egg occurs as a light-gray type in Italy (but never in pure culture) and as a dark-gray type in North Germany, where this race is the only one present in certain areas. The race has been found almost exclusively in low-lying brackish marshes near the sea, or in inland areas where the water has a relatively high salinity. It also occurs in all areas so far studied where malaria is actually or potentially present, and it appears to be relatively more prevalent in dwellings than the other race. It does not go into complete hibernation, but is relatively active in houses and stables throughout the winter even in Northern Europe. In this respect and in others it seems to be the same as *A. maculipennis atroparvus* v. Thiel. It has definite affinities with *A. elutus*. The second race (*A. maculipennis messeae* Falleroni) lays an egg irregularly pigmented in bars and angular patches but including always two heavy transverse bands just distal to the ends of the float structures, which latter are relatively large and long. This race occurs in inland fresh waters in Italy and Germany, in the proportion of 95 per cent of the entire local maculipennis population, and each variation except pure black has been found in pure strains in several regions. It predominates in nonmalarious areas, frequents stables more than dwellings, and goes into complete hibernation in winter. Structural differences between the eggs, larvæ, and male hypopygia of the two races have been described. The use of the egg as a differentiating character should make it possible to classify maculipennis populations and to determine the bionomics of each race and its relation to the transmission of malaria.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 19, 1932

Surface Properties of Intestinal Bacteria Before and After Serum Sensitization.—ELEANORE W. JOFFE, CHARLES H. HITCHCOCK, and STUART MUDD (Department of Bacteriology, School of Medicine, University of Pennsylvania). Data concerning the surface properties of certain strains of intestinal bacteria are presented. A nonflagellate

typhoid strain, 0901, a Flexner dysentery strain, and a strain of *Bacterium enteritidis* have been studied in their smooth and rough variants. The enteritidis bacilli were grown on phenol agar to suppress the flagella. The smooth variants carry surface electric charges so low as to be scarcely measurable, but form even suspensions, insensitive to precipitation by salt. The rough variants grow as a sediment and their suspensions are electrolyte-sensitive, but, paradoxically, they have high surface charges.

Sensitization of these intestinal bacteria with specific immune sera gives them cataphoretic properties presumably approaching those of the antibody protein. Sensitization with rabbit antisera has given the maximally sensitized bacteria isoelectric points between pH 4.8 and 5.2; with horse antisera the isoelectric points have been between pH 4.4 and 4.8. These isoelectric points are well on the acid side of those of normal serum globulins. These results suggest that the antibody globulins against bacteria of this group may be more acid than normal globulins rather than more alkaline like those previously described, such as the antipneumococcus globulin.

Application of Volumetric Methods to the Study of Nonaqueous Cystine Solutions.—T. F. LAVINE and G. TOENNIES (Lankenau Research Institute, Philadelphia). A nonaqueous titration method using sodium methylate as the base, thymol blue as the indicator and chloroform as a diluent was applied to a study of cystin perchlorate solutions in acetonitril. On neutralization by sodium methylate, perchloric acid and cystin perchlorate were indicated by a color change from red to yellow, while acetic acid, ammonium ion, hydrocyanic acid and cystin were denoted by a color change from yellow to blue. Acetic anhydrid in chloroform is also quantitatively neutralized by sodium methylate, mol for mol, the color change of thymol blue being from yellow to blue. The sodium perchlorate formed in the neutralization of perchloric acid was found to affect the first end point leading to low results when the concentration was greater than 0.02 normal.

It was found by titration that acetic anhydrid removes all of the water from a tenth normal cystin perchlorate solution in acetonitril made by the use of 70 per cent perchloric acid, in at least 1 hour.

The decrease in acidity of solutions of 70 per cent perchloric acid in acetonitril was explained by the hydrolysis of acetonitril to ammonium acetate, the reaction being catalyzed by perchloric acid; the acetate reacts basic to perchloric acid forming acetic acid and ammonium perchlorate. A corresponding cystin perchlorate solution is stable, the cystin perchlorate not catalyzing the hydrolysis.

Relation of the Parathyroid Glands to the Toxicity of Irradiated Ergosterol.—JAMES H. JONES (Department of Physiological Chemistry, University of Pennsylvania). Due to the similarity of the pathologic changes produced when either large doses of irradiated ergosterol or parathyroid extract are administered Taylor, Weld, Branion and Kay¹ have concluded that the toxicity of irradiated ergosterol is due to a stimulation of the parathyroid glands. If this conclusion is correct it should be possible to reduce the toxicity of irradiated ergosterol by removing

¹ The Canadian Medical Association Journal, 1931, 24, 763; 25, 20.

the parathyroid glands associated with the thyroid even though accessory parathyroid tissue remained intact. In the following experiments such studies have been conducted. The parathyroids were removed from rats but only those animals which were actually seen in tetany were used for the experiment. The daily dose of irradiated ergosterol necessary to cause death was no greater for the animals from which the parathyroids had been removed than for control animals which retained their complete parathyroid tissue. In like manner the time necessary for any given lethal dose to cause death was no greater for the operated animals than for the controls. Hypercalcemia was also produced as quickly and with as small amounts of irradiated ergosterol in parathyroidectomized animals as in normal unoperated animals. These data indicate that the toxicity of irradiated ergosterol is not due to stimulation of the parathyroid glands.

The Absorption of Glucose from Intestinal Loops.—I. S. RAVDIN, C. G. JOHNSTON and P. MORRISON (Laboratory of Research Surgery, University of Pennsylvania). Solutions of glucose in varying amounts, volumes and concentrations were introduced into jejunal loops prepared by the method by Johnston and the rate of glucose absorption was determined. It was found that with increasing concentrations, there was an increase in the amount of glucose absorbed. Variations in volume had a similar effect in that a marked increase in volume, concentration remaining constant, resulted in an increase in the amount of glucose absorbed.

When volume and concentration were so adjusted that the amounts of fluid removed after a 15-minute period were comparable, the amounts of glucose absorbed were similar when low concentrations were used (below 15 per cent), but were at considerable variance when wide differences (8 per cent to 55 per cent) in concentrations were used. In these experiments there was no relationship between the weight of the animal and the amount of glucose which was absorbed.

Poiseuille's Law and the Capillary Circulation.—EUGENE M. LANDIS (Laboratory of Zoöphysiology, University of Copenhagen). According to Poiseuille's law in the case of a homogeneous liquid flowing through a long tube of small diameter the volume, Q , of liquid which escapes in time, t , is given by the equation,

$$Q = \frac{\pi p r^4}{8 l \eta} \quad (1)$$

where p is the fall of pressure in the tube, r the radius of the tube, l its length and η the coefficient of viscosity. The volume, Q , escaping from a capillary can also be expressed by the equation,

$$Q = \pi r^2 V t \quad (2)$$

where V is the mean velocity per second. Substitution, rearrangement and changing the unit of pressure from dynes per square cm. to centimeters of water yields,

$$p = \frac{8 l \eta V}{980 r^2} \quad (3)$$

The fall in pressure in cms. water can then be calculated for each capillary segment from the length in centimeters, viscosity in dyne seconds or poises per square centimeter, the mean velocity of flow in centimeters per second and the radius in centimeters.

A motion picture camera was used to record the flow of an opaque graphite suspension following blood through the capillary network of the frog's mesentery. The diameter, length and the mean rate of flow were determined for each vessel separately by studying the cinematographic film. The coefficient of viscosity of frog's blood is usually given as 0.0253 and similar figures were obtained by viscosimeter in two observations. This value was used in computing the pressure fall since blood was being displaced from the capillary network while the observations were made.

When thus calculated from Poiseuille's law it appears that the total fall of pressure through the entire capillary network of the frog's mesentery cannot be less than 1.0 to 2.0 cm. of water. According to direct microinjection measurements of blood pressure in single capillaries of the frog's mesentery the average fall in pressure amounts to 4.3 cms. water.¹ The difference between the calculated and the observed figures indicates that the effective viscosity of blood in the capillary network is greater than the viscosity observed when blood flows through the relatively large capillary tubes of the ordinary viscosimeter. Additional evidence that this is the case was found in the literature. Therefore Poiseuille's equation cannot be applied to the capillary circulation except in the limited sense of indicating the lowest possible fall in pressure that can theoretically be associated with the observed rates of capillary blood flow. The true fall in pressure must apparently be determined by direct observations of capillary pressure.

¹ Landis, E. M: *Am. J. Physiol.*, 1926, 75, 548.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MARCH, 1933

ORIGINAL ARTICLES.

FOCAL INFECTIONS IMPLICATING THE NERVOUS SYSTEM.

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THE work of Orr, Rows and others during the past 25 years has revealed to us some of the avenues by which the central nervous system is reached by infections which usually are contiguous in origin to the point of the nervous system attacked, but may often be remote. The general idea that pneumonia may be complicated by a myelitis, that periapical abscess may cause inflammation of distant nerves or roots, such causes and effects are sufficiently familiar to us all. I shall then hardly be able to tell you any new thing, but can point out how the disease picture is determined inevitably by the anatomical pattern so that almost distinct syndromes are evolved. Toxic products or bacterial content pass along set channels: their ultimate destinations are fixed only by tissue barriers and humoral resistance, as the protective dikes of the organism.

One or two characteristic cases will illustrate my meaning:

Case Reports. CASE 1.—A woman in her middle thirties reported monthly attacks of herpes in the skin area supplied by the second and third lumbar roots on the left side. The condition was accompanied by severe pain and appeared on the second or third day before each menstrual period. This phenomenon had been recurring for 2 years. My associate, S. B. Wortis, not content with a dermatologic explanation, discovered a fairly large and infected Bartholin's cyst on the same side as her herpes. We advised surgical excision of this focus. However, she suffered 6 attacks of premenstrual herpes before taking action. Nine months ago she had an attack of herpes and radicular pain before the period following the operation, since when she has been entirely free of symptoms.

TABLE 1.—PATHWAYS OF INFECTION. TONSILLITIS WITH REFERRED PAIN.
Of 182 cases of tonsillitis, 18 (9.9 per cent) had referred pain.

Case.	Sex.	Age.	General symptoms.	Physical exam.	Neurological.	Referred pain.	Organism.	Complication.	Outcome.
1661	M	25	Cough	T (espe. L); P; CN + (L)	Neg.	Chest; L. ear	Pneumoc. (tonsillar smear)	None	Imp.
1675	M	21	None	T; CN + (bilat.); R. ear drum red	Neg.	R. neck; R. ear	Omitted	?Early mitral disease	Imp.
1690	M	35	Cough	T; P; CN + (bilat.); chest rales	Neg.	Under L. ear	Omitted	None	Imp.
1697	F	19	Malaise	T; P	Neg.	Neck; R. ear	Omitted	None	Imp.
1700	M	30	Rigor	T; P; CN + (esp. L)	Neg.	Neck; both ears; both sides of face	Omitted	None	Imp.
1616	M	20	Rigor; cough; herpes, lips; bl. sputum	T; P; CN +	Neg.	Front of head; R. ear	Smear neg.	None	Imp.
1584	F	39	Cough	T; CN + (bilat.)	Aj's: O	L. chest; under R. ear; along R. sterno-mastoid	Omitted	Varicose veins; pregnancy?	Imp.
1590	M	24	None	T	Omitted	R. jaw and down R. neck	Many cocci and bacilli (smear)	None	Imp.
1592	F	53	None	T; P; CN +; perf. both ear drums	Neg.	Front of head; pain L. eye	Omitted	Acute glossitis	Imp.
1611	M	30	Rigor	T; P; CN + (bilat.); L. frontal sinus tender (X-ray neg.)	Neg.	Severe frontal; shooting pains, both ears	Omitted	None	Imp.
815	M	46	Rigor; malaise; gen. pains	T; CN +	Neg.	L. chest	Omitted	Conjunctivitis, acute	Imp.
830	M	23	Rigor; gen. pains	T; P; CN +	Neg.	L. chest	Omitted	None	Imp.
835	M	24	Rigor; malaise; sweating; gen. pns.; bl. sput.	T, esp. R; P; CN + (R)	Deep refl. incr.	Chest; R. ear and R. neck	Omitted	None	Imp.
836	M	29	Rigor; cough; vomiting	T; P	Neg.	L. chest	Omitted	None	Imp.
837	M	20	Rigor; malaise; cough	T	Neg.	Chest	Omitted	None	Imp.
839	M	25	Cough; herpes, lip	T; P; L	Neg.	R. chest	Omitted	None	Imp.
840	M	64	Rigor; cough	T; P	Pupils sluggish; deep refl. incr.	Chest	Omitted	None	Imp.
844	M	30	Malaise; cough; gen. pns.	T (esp. L); P	Neg.	Chest	Omitted	None	Imp.

T = tonsillitis; P = pharyngitis; L = laryngitis; CN + = cervical nodes enlarged.

TABLE 2.—PATHWAYS OF INFECTION. TRANSVERSE MYELITIS.

Of 137 cases of transverse myelitis, 7 (5.1 per cent) were secondary to infection. (Trauma, lues and alcohol, etc.; in most cases the cause was undetermined.) No organisms isolated, except *S. aureus* in Case 19.

Case.	Sex.	Age.	Type of infection.	Pathway.	Spinal cord level.	Duration: 1. From onset. 2. Duration of T. M.	Blood.		Urine.	Spinal fluid.	Out- come.
							W. B. C. (in thousands per c.mm.) and Differential (per cent).	R. B. C. (in millions per c.mm.), Hb. (per cent) and Blood chem.			
50	F	33	Pylonephritis	Lymph or blood	D5	1. ? 2. 370 days	W.B.C. 12.0 P. 85	R.B.C. 0 Hb. 80	1015 Pus +++	Alb. +; glob. +; tp 35-59.6; eg and Was- sermann neg.	Died
51	F	28	Pneumonia (broncho)	Blood	T2-6 Ascending cord soft- ening	1. 76 days 2. ? Imp. after 95 days	W.B.C. 7.7 P. 65 L. 26 Tr. 6 Pne 3	R.B.C. 3.4 Hb. 60 N.P.N. 35 Sug. 80	1038 Negative	eg 221100; sug., glob., Wassermann neg.	Imp.
43	M	55	Pneumonia (uveitis)	Blood	D5-L1 Ascending cord soft- ening	1. 35 days 2. 58 days	W.B.C. 21.0 P. 87	R.B.C. 2.5 Hb. 55 Bl. chem. ng.	1016 Alb. vft.	Bloody (prob. trau- matic); decr. pr.	Died
16	M	41	Embolism (thrombosed internal hem- orrhoids)	Blood	D6	1. ? 2. 48 days	W.B.C. 7.2 P. 70 L. 20 Tr. 8 Eos. 2	Bl. chem. ng.	1010 Alb. +	Glob., sug. and Was- sermann neg.	Died
28	F	22	Abortion (septic)	Blood	Mid-dorsal	1. 5-6 mos. 2. Present on dis- charge; never out of bed after abortion	W.B.C. 13.0 P. 63 L. 27	R.B.C. 4.3 Hb. 85	Neg.	0	Unimp.
19	F	20	Septicemia (infected fin- ger)	Blood	D6	1. 8 days 2. 18 days	W.B.C. 30.4 P. 87	R.B.C. 0	1009 1017 Alb. tr.	Evid. of block; Froin syndrome; cells 100 p. cc.; glob. + + + + Staph. aureus	Died
7*	M	33	Septicemia (infected fin- ger)	Blood (cult. sterile 8 wks. later)	D2	1. ? (chill 8 wks. ago)	W.B.C. 16.0 P. 82	R.B.C. 4.78 Hb. 75	1020 Neg.	Pr. incr.; cells 27; glob. and sug.	Died

* Roentgen ray finger: osteoperiostitis.

TABLE 3.—PATHWAYS OF INFECTION. DIPHTHERIA.

No skin diphtheria found. Of 294 cases of diphtheria, 13 (4.4 per cent) showed involvement of the nervous system.

Case.	Sex.	Age.	Focus of infection.	Culture.	Paralysis; with days after onset in parens.	Antitoxin given; days after onset in parens.	Outcome; days after onset that paralysis cleared up in parens.
5728 . .	M	4½	T	Pos.	P (33); MC	20,000 U. (1) 10,000 U. (3)	47 (death)
3438 . .	M	27	T	Pos.	P (21); E (?); PN (?); MC	20,000 U. (21) 10,000 U. (42)	P and E? (14S); ?PN
1286 . .	M	5	T; N	Pos.	P (8)	20,000 U. (4)	P? (24)
341 . .	M	2½	T; N	Pos.	P (11); MC	15,000 U. (2)	P? (31)
5668 . .	M	S	T	Pos.	P (20)	25,000 U. (5)	P (62)
3518 . .	M	1½	T; N; L	Pos.	P (42); E (?); PN (?); neck weak	30,000 U. (3)	P (74); E? (74); PN? (74)
4934 . .	M	2½	T	Pos.	P (38); PN (38)	20,000 U. (3)	41 (death)
1378 . .	M	5	T; N	Pos.	P (11); E (50); MC	5,000 U. (2) 10,000 U. (3) 5,000 U. (4)	P and E until death (56)
3192 . .	F	3	T; N	Pos.	P (18); PN and incontinence (?)	25,000 U. (8)	P (52); PN and still incont. on discharge
861 . .	M	19	T; N	Pos.	P (40); E (40); PN (59)	30,000 U. (3)	P and E (54); PN present on discharge (79)
899 . .	F	5	T; N	Pos.	P (12); peripheral facial (12); E (9); MC	15,000 U. (4)	14 (death)
2255 . .	F	2	T; N	Pos.	P? (27); PN? (27); MC; neck weak	20,000 U. (4)	46 (death)
? . .	M	3	T	Pos.	P? (21); PN (42); back weak	10,000 U. (1)	While in hospital

T = throat; N = nose; L = larynx; P = palate; E = Eye; PN = peripheral neuritis; MC = myocarditis.

CASE 2.—A man seen in the middle West some years ago was presented as a case of amyotrophic lateral sclerosis. For 2 months he had had progressive ascending weakness of the legs with so-called rheumatic pains and disturbance of sphincter control. Wasting and fibrillary twitching of the thigh muscles were dominating features of his condition. Nothing abnormal was found in the arms, a peculiarity which, added to bladder involvement and shooting pain in the legs, cast doubt on the original diagnosis. A rectal examination gave evidence of a firm but fluctuating mass in the prostate which was correctly diagnosed as abscess and evacuated. Complete sphincter control was reestablished within a month and progressive recovery in motor function followed.

CASE 3.—A middle-aged officer had 8 teeth removed, following local novocain infiltration of the gums. Three days later he began to suffer from severe pain in the back of the neck and violent headache. Progressive signs of meningitis developed, which were confirmed by finding streptococci in the spinal fluid. Death occurred within 3 weeks despite the giving of antimeningococcus serum and frequently repeated blood transfusions.

It may be said here that the morbid process in these cases could scarcely have been recognized had not the general plan of drainage

TABLE 4.—PATHWAYS OF INFECTION. CAUDA EQUINA NEURITIS.

The following cases are selected from 765 cases of "neuritis," i. e., all forms of neuritis except polyneuritis.

Case.	Sex.	Age.	Focus of infection.	Organism.	Probable pathway.	Sp. cord seg.		Onset after focal infection: Time interval.	Laboratory.	Roentgen ray.	Operative findings.	Outcome.
						ments or peripheral nerves involved.						
315*	F	16	Probably perineal infec.	? Gc (pos. vag. smear infec. 2 mos. prev.)	Lymph	S1-4	5 mos.		Temp. 103.6°; alb. pus; R. B. C. 3.6 million; hb. 70%; W.B.C. neg.; bl. chem. neg.	Swollen, glossy, red roots with adhesions	Slight imp. after oper.
296	M	45	Influenza	?	? Blood	Approx. L1	Immed. after influenza 8 yrs. prev.		Temp. 100.2°; bl. not done	Sl. hypertr. arthr.; L5 vert.	No oper.; lum. punct. neg.	Unimp.
370†	F	43	?	?	Prox. inflam. re- action	Lower lumbosacral	Immed. after hysterectomy 4 yrs. prev.		Temp. 101°; alb. ++; few W.B.C.; bl. count not done; bl. Wass. neg.	Suggestive lesion, L5 vert.	No oper.	Unimp.
169†	M	55	?	?	?	L5-S1	(?) Symps. 7 mos. before adm.		Temp. 104°; Alb. ++; W.B.C. and R. B. C.; W. B. C. 14,200; PS5, T5, L10	Agglut. C.-E. route: pseudo tumor	Imp. after oper.
215	M	70	Influenza	?	? Blood	Lumbosacral roots	(?) Immed. after exposure to bad weather		Temp. 98.8°; bl. Wass. neg.; bl. chem. neg.	Not done	No oper.	Unimp. after 3 days in hosp.
221	F	40	Influenza	?	Blood	Lumbosacral roots	(?) Immed. following influenza 3 mos. prev.		Temp. 97-99°; pus; R.B.C. 3.23 millions; hb. 80%; bl. chem. neg.	Dissect. atrophy of long bones	No oper.	Imp. after 84 days
230	M	28	Influenza	?	Blood	Lumbosacral radiculitis	(?) Following influenza 1 yr. prev.		Temp. 99°; R.B.C. 5.32 million; hb. 86%; bl. Wass. neg.	Pelvis and spine neg.	No oper.	Imp. after 11 days

* Surgically proven case. † Bony disease. ‡ Surgically proven case. Lumbar puncture negative. Lipiodol showed obstruction level L4.

TABLE 5.—PATHWAYS OF INFECTION. MENINGITIS SECONDARY TO INFECTIONS ABOUT THE HEAD.
Of 422 cases of meningitis, 24 (5.7 per cent), were secondary to infection about the head.

Case.	Sex.	Age.	Site of infection.	Organism: 1 = Primary infection. 2 = Spinal fluid. 3 = Blood.	Involvement of nervous system.	No. of days after infection meningitis appeared.	Pathway.	Treatment.	Outcome.
67 . .	F	8	Abscess, L. eyelid; panophthalmitis	1. Staph. 2. Neg. 3. Gram-pos. dip.	Cav. sinus thrombosis; meningitis	5th day	Lymph or blood (venous)	Antimening. serum 6th day; incis. abscess	Died 9th day
84 . .	M	15	Abscess of upper lip	1. Staph.? 2. Gram-pos. cocci 3. Staph.	Cellulitis of face; meningitis	Approx. 7th day	Lymph or blood	No serum	Died 9th day
50 . .	M	29	Furuncle of L. nose	1. Staph.? 2. Neg. culture 3. Staph.	Cav. sinus thrombosis; meningitis	3d day	Lymph or blood	No serum	Died 5th day
73 . .	F	12	L. ear	1. Omitted 2. Strep. and staph. (smear) 3. Omitted	Epidural abscess (oper.); meningitis	O. M. P. C., sev. mos.; convulsions night before	Direct or lymph or blood (venous)	No serum; mastoidectomy	Died 21 days after adm.
88 . .	F	37	Abscess of L. ear	1. Omitted 2. Omitted 3. Omitted	Meningitis	O. M. P. C., 27 days	Direct or lymph or blood (venous)	No serum	Died about 33d day
8 . .	F	10	Cellulitis of R. orbit	No tap or culture (prob. strep.)	Meningitis	2d day	Lymph or blood	No serum	Died 5th day
59 . .	F	34	O. M. P. A., bilateral.	1. Hemol. strep. and staph. 2. Non-hemol. strep. 3. Omitted	Meningitis	Approx. 14th day	Direct or lymph or blood	No serum; bilat. myringotomy	Died 28th day
65 . .	M	15	O. M. P. C., R.; abscess in front of R. ear	1. Strep. (swab from oper.) 2. Gram-pos. pneum. (confirmed by mouse injection) 3. Neg.	Softening of brain tissue (abscess)	? 7th day	Lymph or blood	No serum; abscess drained	Died 46th day

69	M	6½	O. M. P. A., R.	1. Staph. aureus 2. Nonhemol. strep. 3. Omitted	Meningitis	Approx. 14th day	Direct or lymph or blood	No serum; mastoidectomy	Died 25th day
53	M	57	Carbuncle, R. neck (angle of mandible)	1. Staph. aureus? 2. Neg. 3. Staph. aureus	Meningitis	295th day	Lymph or blood	No serum	Died 301st day
7	M	49	Carbuncle back of neck	1. Neg. 2. Neg. 3. Not done	Osteomyel., epimening., mening., myelomal. (P.M., R. cerebell. and spinal cord C4-5)	12th day	Lymph	No serum; decompr. laminec.	Died 61st day
10	M	14	O. M. P. A., L.	1. Pneumo. (smear) 2. Gram-pos. diplo., mostly extracell. 3. Omitted	Meningitis (P.M., green fluid at base)	5th day	Direct or lymph or blood	No serum	Died 5th day, 3½ hrs. after adm.
18	M	59	O. M. P. A., L., foll. extract. of carious teeth	1. Pneumo. (P.M., ear) 2. Pneumo. (smear) 3. Omitted	Meningitis (P.M., pneumo. mening. fluid over brain)	3d day	Direct or lymph or blood	No serum	Died 7th day
19	M	24	Abscess of L. cheek foll. extract. of tooth	1. Omitted 2. Omitted 3. Omitted	Septicemia; spin. fluid clear; ?abscess of brain	12th day	Blood	No serum	Died 22d day
20	F	62	P. M. P. C., R., with acute exacerb.	1. Pneumo. (P.M.) 2. Pneumo. 3. Omitted	Meningitis (P.M., leptomening. of base)	2d day	Direct or lymph or blood	No serum	Died 6th day
21	M	31	Furuncle in L. ear	1. Neg. 2. Neg. 3. Omitted	Serous meningitis (sterile)	Approx. 31st day	Lymph or blood	No serum	Neur. neg. 79th day; otitic hydrocephalus

TABLE 5.—PATHWAYS OF INFECTION. MENINGITIS SECONDARY TO INFECTIONS ABOUT THE HEAD.—(Continued.)

Case.	Sex.	Age.	Site of infection.	Organism: 1 = Primary infection. 2 = Spinal fluid. 3 = Blood.	Involvement of nervous system.	No. of days after infection meningitis appeared.	Pathway.	Treatment.	Outcome.
13 . .	F	28	O. M. P. A., L.	1. Omitted 2. Pneumo. 3. Neg.	Meningitis	Ca. 7th day	Lymph	No serum	Died 8th day
17 . .	M	26	L. cheek, acute purulent max- illary sinusitis	1. Omitted 2. Omitted 3. Neg.	Upper cord? toxie from myelitis; sp. fluid 15 cells; an- csth. L. face; neck stiff	Ca. 9th day	Lymph or blood	No serum	Died 56th day
20 . .	F	35	Ulcer R. cheek; max. sinu. foll. extraction of teeth; cellulitis R. orbit	1. Pneumo. (P.M.) culture 2. Pneumo (P.M.) 3. Neg.	Meningitis (P.M.)	Ca. 20th day	Direct or lymph or blood	No serum	Died 22d day
43 . . (D1)	F	28	O. M. P. A., bi- lateral	1. Omitted 2. Staph. and strep. (smear) 3. Omitted	Extradural absc.	Ca. 60th day	Direct or lymph	No serum; mas- toidectomy, bi- lateral	Died 63d day
43 . . (D3)	M	42	O. M. P. A., R.	1. Strep. 2. Strep. 3. Omitted	Meningitis	No history, pa- tient in coma	Direct or lymph or blood	No serum; my- ringotomy, R.	Died within 24 hrs. after adm.
5 . .	M	50	O. M. P. A., L.	1. Pneumo. (P.M.) 2. Pneumo. (P.M.) 3. Omitted	Meningitis	No history, pa- tient in coma	Direct or lymph or blood	No serum	Died within 24 hrs. after adm.
10 . .	F	38	O. M. P. A., R.	1. Omitted 2. Strep. hemolyticus (smear and cult.)	Meningitis (P.M.), ac. pur. mening.	18th day	Lymph or blood	No serum	Died 21st day

pathways to the nervous system from infected areas been previously hypothesized and later proven. Indeed, one feels that the comparative paucity of infecting foci found in our Bellevue groups of nervous system infections may be due to the absence of the correlation of cause and effect in the minds of the examiners.

In a careful reading of the records of 182 cases of acute follicular tonsillitis, there were found 18 (9.9 per cent) in which severe referred pain was a prominent symptom. All such cases were adults, probably because children localize pain poorly. The distribution of pain was in order of frequency: the ears (local disease was absent), the chest wall, the face and neck. In short, these severe referred pains occurred in the area of distribution of the fifth nerves and the upper cervical roots. An appreciation of the significance of these pains would make needless many puncturings of normal eardrums and sinuses.

A review of 294 cases of nasopharyngeal-laryngeal diphtheria admitted to Willard Parker Hospital and treated with antitoxin at varying intervals from the beginning of the disease showed that 4.4 per cent had involvement of the nervous system. The symptoms in the order of frequency were palatal palsy, palsy of accommodation, polyneuritis. Death in most cases was attributed to myocarditis.

Nearly all these neural cases were heavily treated—20,000 and 30,000 units—but too late. Apparently, absorbed diphtheria toxin combines readily with nervous tissue and forms a stable product, in that subsequent enormous doses of antidiphtheritic toxin avails little to reduce neural symptoms. Some of the polyneuritic cases complicating diphtheria were difficult to differentiate from poliomyelitis, in that thoracic and cervical radiculitis produced weakness of related muscle groups and sacral root involvement occasionally resulted in sphincter paralysis.

No cases of skin diphtheria could be found as such in the Bellevue or Willard Parker records. However this aspect has been well studied by Walsh in troops on active service in Egypt. Here so-called "desert-sores" occurred commonly from which Klebs-Loeffler bacilli were recovered in almost pure culture. A vast number of cases of polyneuritis ensued.

The most important observation made by Walsh was that invariably there was an initial local paresis related anatomically to the site of the infected focus, a fact which forbids the notion that in such conditions the toxin is carried entirely by the blood to the nervous tissue. No case of extrafaucial diphtheria had paralysis of the palate.

Two of his cases may be mentioned here:

CASE 4.—An artillery driver suffered from multiple septic sores on the thighs and buttocks and a large ulcer of the perineum. After 7 weeks he began to have numbness on the buttocks and around the anus. This numbness spread to the penis, scrotum, and the backs of the thighs; a few days

later there was loss of control of the bladder and rectum. Not until weeks afterward was there general polyneuritis, by which time there was also deterioration of visual convergence. On examination, he was found to have complete loss of all forms of sensation over the 4th and 5th sacral root areas and partial loss over the 2d and 3d sacral root areas.

CASE 5.—A medical officer infected his right thumb while performing a tracheotomy on a fatal case of laryngeal diphtheria. The finger wound healed in 7 weeks, but he began to notice numbness and loss of feeling in the affected thumb; this numbness spread to the radial part of the hand. Also ataxia and weakness developed in the right arm. After these disabilities he sustained a generalized multiple neuritis, but had no accommodation paralysis.

An examination of the Bellevue records of 765 cases diagnosed as neuritis (but not including polyneuritis) revealed a group of 7 cases of severe cauda equina neuritis 5 of which immediately followed influenza; 1 case was secondary to gonococcal infection of the perineum, and another followed hysterectomy. I feel sure that ascending neuritis of the cauda equina occurs more frequently than hospital records would seem to show; suspicious cases in the gynecologic and urologic fields should be rigorously examined.

Of 137 cases of transverse myelitis studied, 5.1 per cent were secondary to a known infection; in most cases the cause was undetermined. Pneumonia was responsible for 2 gradually ascending softenings on the dorsal cord. Two upper dorsal transverse lesions were secondary to infected fingers. A thrombosed internal hemorrhoid furnished the focus in the fifth case and a septic abortion in yet another. It would appear that in this group the blood stream is the path of access to the spinal cord; the dorsal cord would seem especially susceptible to attack and one remembers that this also holds good for Pott's disease of the spine.

Infections about the head accounted for 5.7 per cent of 422 cases of meningitis studied from the Bellevue records. Fifteen were secondary to infections of the middle ear; 1 of these was a case of serous meningitis with hydrocephalus; 2 followed orbital infections; 2 followed carbuncle of the neck and 2 sinusitis; 1 came from a cheek abscess and 1 from a furuncle of the nasal mucous membrane. The last proceeded from a cellulitis of the upper lip.

With the exception of the case of otitic hydrocephalus, all were fatal: a mortality which emphasizes the necessity of treating infections about the upper face by wet dressings and drainage rather than by incision.

The details of these cases are presented in chart form. These neural complications of focal infection are nothing more than the commonplaces of hospital experience; to know that they occur in bulk will impose on us the need of search for prime causes in conditions apparently more obscure.

NOTE.—My sincere thanks are due Miss Sarah Shiras for her great help in the statistical investigation of several thousand case records.

TUMORS OF THE GASSERIAN GANGLION.*†

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(From the D. J. McCarthy Foundation of the University of Pennsylvania.)

THE severe symptoms accompanying tumors of the Gasserian ganglion have resulted in recognition of the condition for many years. Among the earliest case reports, Sachs¹ has mentioned 1 by Dixon in 1846 and 1 by Günsburg in 1848. Peet² refers to a primary tumor studied as early as 1836, by R. W. Smith, and reported in 1849. Peet found a total of 63 cases in the literature in 1927. Additional cases are 1 of Parker,³ 2 reported by Russell,⁴ a case of Rand,⁵ 2 of Altmann,⁶ 1 of Gaines,⁷ 1 of Learmonth and Kernohan,⁸ Bradley and Smith⁹ and 1 which was studied in the respective services of Dr. Spiller and Dr. Frazier and reported by the author.¹⁰ Cadwalader¹¹ has reported a tumor which arose in the immediate neighborhood of the Gasserian ganglion and completely embraced the sensory root, causing symptoms characteristic of a tumor arising in the ganglion itself. This gives a total of 76 reported tumors, including Peet's 2 cases and the 1 of Cadwalader.

Tumors of the Gasserian ganglion are relatively rare. Frazier¹² had performed major operations on more than 300 patients suffering from tic douloureux up to 1918 and at that time had encountered only 3 instances of tumor involving the Gasserian ganglion. Cushing,¹³ in 1920, had found 4 primary and 4 secondary tumors causing symptoms referable to the ganglion in his series of 550 verified intracranial tumors. In the files in the Neuropathologic Laboratory of the Philadelphia General Hospital, the author has found 4 instances of primary or metastatic tumor involving the Gasserian ganglion in the records of almost 5000 cases. These records are composed largely of the neuropathologic findings at autopsy in various types of cases in which disease of the nervous system had been suspected during life, and a small percentage of reports based upon the findings in biopsy material obtained at operation.

Case Reports.† CASE 1 (Univ. Hosp., Surg. No. 11516 and No. 12069).—C. P. C., a male, aged 47 years, was admitted to the service of Dr.

* Based on material from the Neurologic, Neurosurgical and Neuropathologic Departments of the Hospital of the University of Pennsylvania, and the Neurologic, Radiologic and Neuropathologic Departments of the Philadelphia General Hospital.

† Read in abstract at a meeting of the Philadelphia Neurological Society, February 26, 1932.

‡ Drs. William G. Spiller, Charles H. Frazier, J. B. Carnett, B. J. Alpers, F. C. Grant and N. W. Winkelman have kindly given the author access to the records and material in their respective departments for the purpose of this report. The cases described herein are taken, as indicated, from these sources.

Frazier on August 16, 1927, complaining of pain in the left side of the face. The onset had been with pain in an upper left premolar tooth 13 months previously. It had increased in extent until at the time the patient came under observation, it involved the entire left trigeminal distribution. The pain was almost constant, but there also occurred acute paroxysms of tic-like pain 3 or 4 times daily. The patient had had the left infraorbital nerve sectioned previously, and there was some hypesthesia of the face which was supposed to be the result of this operation. The motor branch of the trigeminus was unaffected and the cornea was not anesthetic. There was some defect of hearing in the left ear which was attributed to a chronic otitis media. The examination was otherwise negative.

Dr. F. C. Grant surgically exposed the Gasserian ganglion. A discrete tumor of the ganglion, probably involving the 7th cranial nerve also, and eroding the petrous portion of the temporal bone, was found and removed. The excised tumor mass measured 2 cm. by 1.5 cm. by 0.5 cm. Dr. Winkelman reported that it showed, microscopically, remnants of what was probably Gasserian ganglion here and there, with much-altered ganglion cells. The entire section was overrun with connective tissue, with areas of calcification scattered throughout. The tissue was very cellular with numerous small round nuclei. Most of the cells were not unlike lymphocytes in appearance; others had irregular elongated nuclei, definitely young connective-tissue elements. Scattered throughout the tissue were small islands of cells with large vesicular nuclei containing faint chromatin granules.

Microscopically, Dr. Winkelman stated, "the nature of these abnormal cells, most of which are arranged in islands, is doubtful. They are probably identical with the capsule cells of the ganglionic elements and superficially resemble endothelial elements, even though they are in all probability ectodermic in origin. There has been a recent tendency to label tumors of this sort 'Schwannomas' or sheath neuromas. There are present here also cells of a chronic inflammatory nature, such as have been described in other tumors of this sort."

At the time of discharge there was some residual pain referred to the left cheek and the mouth, described by the patient as deep "bone pain," and there was left 7th nerve palsy.

About 4 weeks later, a difficulty in swallowing and an impairment of speech had developed, and the pain had become much worse again and had spread from the face to the occiput. Enlarged submaxillary lymphatic nodes had appeared by the time he was seen again, 7 weeks after the operation, and at that time there was complete left 5th, 7th, 9th, 10th and 12th nerve palsy, and partial bilateral 8th nerve involvement, more on the left side. A roentgenogram showed some atrophy of the dorsum sellæ. Dr. Grant then exposed and removed a tumor in the posterior fossa, situated directly over the posterior lacerated foramen. The tumor measured 1 cm. by 5 mm. by 7 mm. and showed the same microscopic structure as the tumor of the Gasserian ganglion. Death occurred Nov. 17, 1927.

CASE 2* (Univ. Hosp., Neurol. No. 71898; Surg. No. 3089).—W. M., a male, aged 34 years, was admitted to the service of Dr. Spiller on February 19, 1924, complaining of headache, numbness of the left side of the face, and weakness of the lower extremities. The onset had been with headache, vertigo, pain in the left side of the face and impairment of vision about simultaneously 1 year before admission. For 6 months he had been subject to occasional transient fainting attacks, and during the period of observation a Jacksonian attack affecting the right arm and leg occurred. There

* This case was reported by Dr. F. C. Grant at the meeting of the Philadelphia Neurological Society of May 25, 1924. As his report was not published in the Society Transactions, he has kindly permitted the author to include the case in this communication.

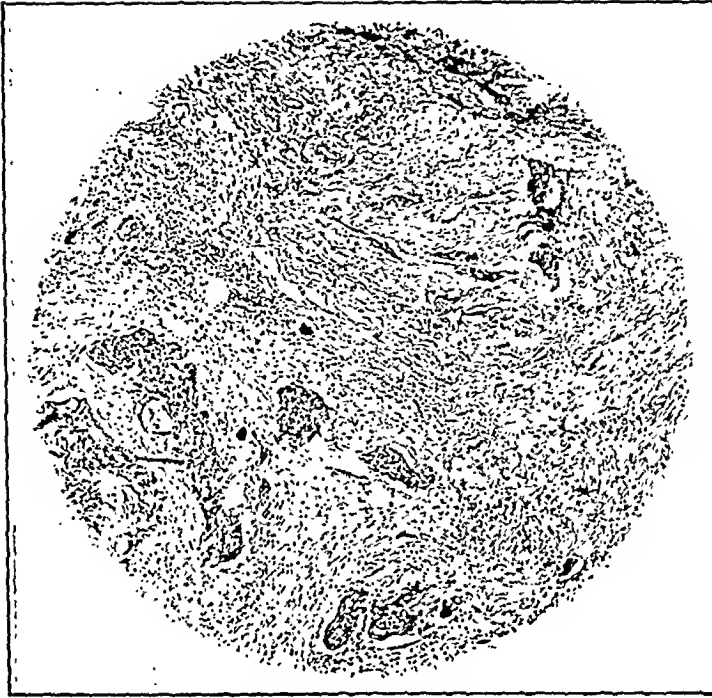


FIG. 1.—Section of the Gasserian ganglion of Case 1, showing the fibrosis, the inflammatory cell infiltration, and the nests of tumor cells.



FIG. 2.—Photograph of the patient (Case 1) showing the borders of the postoperative area of anesthesia in the trigeminal distribution marked by ink lines.



FIG. 3.—Case 2, a section from the Gasserian ganglion showing the primitive type of cells, many of which are arranged in globular groups.



FIG. 4.—Case, 3, a section from the Gasserian ganglion showing the dense fibrous background, the inflammatory reaction, and the islands of tumor cells which have the appearance of young fibroblasts.

was a history of a luetic infection at the age of 23. The examination showed a hyperalgesia of the left forehead and cheek, a diminution of the recognition of touch on part of the left forehead, but not on the cheek, and a diminution of the left scleroconjunctival reflex. The lachrymal reflex was distinct. At times there was a slight impairment of pain and temperature sensation in part of the distribution of the first division of the left trigeminus. There was slight ocular sympathetic involvement on the left. The left masseter and temporal muscles were weak and there was slight weakness, peripheral in type, of the left side of the face. A Bárány examination by Dr. L. Fisher gave findings very suggestive of a left cerebellopontile angle lesion. The tendon reflexes were hyperactive, more so on the right side, and there was abortive ankle clonus on the right. The blood Wassermann was positive.

Dr. Grant exposed the left Gasserian ganglion and found and removed a tumor of the ganglion. He thought at that time that the growth involved the posterior fossa as well, since neoplastic tissue apparently accompanied the sensory root.

Dr. J. McFarland has reported on the fragments of tissue removed at operation. "The sections are of an embryonal type of tumor of nervous origin representing an early stage of development, containing numerous globes of cells such as characterize the neurocytomas, very closely related to or resembling the equally primitive brain tumor called medulloblastoma. They are malignant both by invasion and by metastasis. The tissue also most closely resembles the retinoblastoma or glioma of the retina." His diagnosis was neurocytoma.

Roentgenologic and antiluetic treatments were carried out subsequently. Eleven months after operation, the patient had some epileptiform attacks. Examination about that time showed an elevation of the optic disks of 1 diopter. Except for an increased degree of mental sluggishness and a complete motor and sensory 5th nerve paralysis on the left, the neurologic examination showed no marked changes over previous examinations. The cerebrospinal fluid Wassermann, which had been negative previously, was then positive. After that time, contact with the patient was lost, and the final outcome is not definitely known.

CASE 3 (Univ. Hosp., Surg. No. 22072).—L. C., a male, aged 33 years, was referred to the service of Dr. Frazier by Dr. M. C. Thrush on June 27, 1931. He complained of pain in the right side of the face and blindness in the right eye. The onset had been in November, 1930, with pain in the upper gum. A tooth had been removed for the relief of the pain, but on the same day severe pain in the malar region had developed, and within a month had involved the entire right side of the face and the side of the head. Impairment of vision had begun simultaneously with the onset of the pain and had progressed to complete blindness in the right eye within $3\frac{1}{2}$ months. Prominence of the right eyeball had been noticed 1 month after the onset. The speech had been impaired for a short time before he entered the hospital. An alcohol injection 6 weeks before admission had failed to relieve the pain. There had been some anorexia and occasional vomiting, and he had lost weight, but the duration of these symptoms was uncertain. He described the pain as a "hard, throbbing ache" which was constant and was becoming worse. This pain was limited to the distributions of the second and third divisions of the right trigeminal nerve, but in addition to this there occurred, each afternoon, a bitemporal headache which lasted for 4 or 5 hours.

The general *physical examination* was essentially negative. The patient had a tendency to sleep much of the time, and was not entirely coöperative. The speech was mumbling in character and almost unintelligible. The Romberg was positive, and the gait unsteady. Skilled movements were

poorly executed and there was rather marked adiadochokinesis of the right hand. The motor power was generally reduced without any marked difference on the two sides and with no distinct paralysis of any limb. The tendon reflexes were about normal on the two sides, and there were no pathologic reflexes. The right eye was entirely blind and there was primary optic atrophy on this side. The vision in the left eye was 6/9. There was weakness of the right external rectus muscle, the internal rectus, and possibly a little bilateral ptosis. The right pupil was dilated and reacted sluggishly to light and in convergence. Exophthalmus of the right eye was present.

Hyperesthesia in the right trigeminal distribution was noted, but no loss of sensation could be demonstrated. The corneal reflex was present on each side, but that of the right side may have been a little sluggish. The masseter, temporal and pterygoid muscles were equally innervated. The sense of taste was normal. No demonstrable impairment of function of the other cranial nerves could be demonstrated, although the speech was decidedly thick. The patient was left-handed.

The blood Wassermann test was negative. The cerebrospinal fluid was under pressure of 120 mm. of water, contained 14 cells per c.mm., showed an increased protein content, a negative Wassermann reaction, and a colloidal gold curve of 0001110000.

The roentgenograms showed a normal pituitary fossa. The encephalogram after injection of air indicated that the ventricles were top normal in size. The subcortical markings were almost completely absent on both sides, and a few dilated pathways were seen in the right posterior parietal region. Dr. Kornblum interpreted the findings as indicative of obstruction and dilatation of the pathways in the region of the Island of Reil on both sides, somewhat more marked on the right side.

The patient left the hospital on July 15, 1931, and he declined to return for further observation or treatment. Subsequently, he was admitted to another hospital where apparently an exploratory operation was done, but the tumor was not removed. Death occurred in December, 1931.

Pathologic examination (Dr. B. J. Alpers) was obtained through the courtesy of Dr. E. A. Dougherty. There was an operative incision in the dura over the right frontal lobe. Within the folds of, and under the dura on the inferior and lateral surfaces of the right temporal lobe was a firm dumb-bell shaped tumor involving the Gasserian ganglion, being continuous with the central trigeminal root. Half of the tumor seemed to be enshrouded in two folds of dura, possibly the two folds of Meckel's space. The other half lay under the dura. There was considerable thickening of the tentorium on the left side. Microscopically the tumor was encapsulated, and scattered in its substance were small clusters of degenerated ganglion cells and irregular bundles of nerve fibers surrounded by Schwann cells. In the tumor there was an exceedingly dense background of collagenous and fibrous tissue, through which were scattered islands of tumor cells completely surrounded by fibrous tissue. The cell clusters were solid in some areas, and in others there was central degeneration, resulting in an acinar appearance. The clusters were composed of young fibroblasts, cells with round nuclei of moderate size, occasional polymorphonuclear cells, and fairly numerous cells with fragmented nuclei. It appeared to Dr. Alpers that young fibroblasts were growing from the fibrous walls into the cellular islands. The microscopic diagnosis was fibroblastoma.

Discussion. The diagnosis of tumors of the Gasserian ganglion must be governed by the appearance of such symptoms and signs as have been observed by careful clinicians in other verified cases. The usual symptomatology has been described in detail by many authors, among whom may be mentioned Spiller,¹⁴ Cadwalader,^{11,15}

Frazier,¹² Cushing,¹³ Sachs,¹ and Peet.² Pain in the distribution of the trigeminal nerve of the side of the lesion, usually occurring early in the course of the disease, having a dull and constant quality, sometimes with paroxysms of acute tie-like pain, has been stressed repeatedly. The objective diminution or loss of the sensations of touch, pain, heat and cold in a part or all of the ipsilateral trigeminal distribution is considered common, the combination of spontaneous pain and impairment of sensation objectively (anesthesia dolorosa) being regarded by many as diagnostic of tumor in the absence of syphilitic or tuberculous infection. Diminution of the scleroconjunctival reflex on the same side, loss of the lacrimal reflex and the gag reflex, impairment of taste on the anterior part of the tongue, and impairment of function of the motor branch of the trigeminus and of the nerves supplying the intrinsic and extrinsic muscles of the eye are not unusual. With the extension of the growth to invade or compress the cerebral tissue or the structures of the posterior fossa, additional symptoms and signs occur, dependent upon the structures affected.

That the diagnostic criteria usually emphasized do not occur in every case of tumor of the Gasserian ganglion was suggested, however, by the indistinctness of the signs in Cases 1 and 3 and by the fact that Hellsten's¹⁶ review of the literature in 1914 and Frazier's¹² analysis of 29 cases in the literature up to 1918 indicated that the occurrence of symptoms and signs definitely referable to neoplastic disease of the ganglion had not been observed as frequently as one would expect. Consequently, the author analyzed the available recent case reports, together with some of the earlier ones in which detailed studies had been recorded, in order to determine the clinical findings and the results of treatment in a more uniformly studied series. For the purpose of this analysis only verified cases of tumor arising in the ganglion or its immediately adjacent sheaths, and such secondary tumors as had invaded the nervous tissues only in the immediate neighborhood of the ganglion were included. The cases of Peet² and of Woltman¹⁷ were omitted from the statistical study because of the probable involvement of the peripheral branches of the trigeminus prior to actual ganglion invasion.

The more important features described in the reports included in this study are summarized in Table 1. Under the heading of "Initial Symptoms" are listed those manifestations which occurred first in the course of the disease or so soon after the onset as to make them practically indistinguishable from the first symptom. Under "Objective Findings" are listed the important neurologic signs observed in the study of the patients and ascribed to the effects of the tumors.

A more detailed analysis of these 22 cases (Table 2) gives the frequency of occurrence of the various manifestations.

TABLE 1.

Author.	Reference.	Initial symptoms				Objective findings.						
		5th nerve pain.	5th nerve numbness.	5th motor weakness.	Other symptoms.	Sensory loss (5th).	Motor weakness (5th).	Hyperesthesia (5th).	Impaired reflexes (5th).	Impaired taste.	Sympathetic signs.	Signs not related to 5th nerve disease.
Spiller, Case 1	14	+	..	+	..	+	+	..	+	+	..	+
Spiller, Case 2	14	++	+	+	+	+
Plummer and New	18	++	+	+	..	+	+	..	+
Sachs	1	++	+	..	+	..	+	+	..	+
Percy	19	++	+	+	..	+	+	..	+
Cadwalader	11	+	+	+	..	+	+	..	+
Cushing, Case 328	13	+	+	+	..	+	+	..	+
Shelden, Case 1	20	+	+	+	..	+	+	..	+
Shelden, Case 2	20	+	+	+	..	+	+	..	+
Shelden, Case 3	20	+	+	+	..	+	+	..	+
Parker, Case 4	3	++	+	+	+	+	+	+	..	+
Rand	5	+	+	+	..	+	+	..	+
Russell, Case 1	4	..	+	+	+	+
Russell, Case 2	4	+	+	+	+
Altmann, Case 1	6	+	+	..	+	+	..	+
Altmann, Case 2	6	+	+	..	+	+	..	+
Gaines, Case 2	7	+	+	+	+	..	+	+	..	+
Learmonth and Kernohan	8	+	+	+	..	+	+	..	+
Cooper	10	+	+	+	..	+	+	..	+
Case 1 of this report	..	+	+	+	..	+	+	..	+
Case 2	..	+	+	..	+	+	+	+	+	+	+	+
Case 3	..	+	+	+	+	+	+	+	..	+
Totals	..	17+	3	1	10+	16+	13+	5	10+	4	3+	21

TABLE 2.—ANALYSIS OF 22 CASES.

Initial Symptoms:

Pain in the ipsilateral trigeminal distribution	17 times
Ipsilateral trigeminal pain (possibly not initial)	1 time
Ipsilateral numbness in trigeminal distribution	3 times
Ipsilateral trigeminal motor weakness	1 time
Impairment of vision	4 times
Nausea, vertigo, tinnitus or impaired hearing	4 times
Headache	3 times
Diplopia or ptosis	2 times
Cervical lymph node enlargement	2 times
Paresis of extremities	1 time

Objective Findings:

Impairment or loss of touch, pain, heat or cold sensations in ipsilateral trigeminal distribution	16 times
Trigeminal sensory impairment of doubtful etiology	1 time
Ipsilateral trigeminal motor weakness	13 times
Questionable ipsilateral trigeminal motor weakness	2 times
Hyperesthesia or hyperalgesia in ipsilateral trigeminal distribution	5 times
Diminution or loss of ipsilateral conjunctival reflex	10 times
Ipsilateral impairment of taste on anterior part of tongue	4 times
Diminution of ipsilateral lacrimal reflex	1 time
Ipsilateral impairment of sympathetic function	3 times
Questionable sympathetic impairment	2 times

Objective Findings Referred to Other Cranial Nerves:

Ipsilateral 3d, 4th, or 6th nerve involvement	15 times
Ipsilateral 8th nerve involvement	9 times
Ipsilateral impairment of hearing (doubtful etiology)	4 times
Ipsilateral 7th nerve involvement	8 times
Ipsilateral 9th or 10th nerve involvement	4 times
Questionable 9th or 10th nerve involvement	1 time
Ipsilateral 12th nerve involvement	4 times

Other Signs:

Enlargement of cervical lymph nodes	6 times
Ipsilateral exophthalmus	4 times

Although such an analysis as this, based upon reports by different observers whose findings necessarily were subject to individual variations, cannot be precise and all-inclusive, nevertheless it gives reasonable assurance that no single symptom or sign occurs invariably. In 3 cases (Cushing,¹³ and Altmann's⁶ 2 cases) the initial symptoms had no suggestion of trigeminal disease; and in another (Shelden's²⁰ Case 2) tinnitus of undetermined cause preceded the 5th nerve symptoms by $1\frac{1}{2}$ years. In 2 instances (Sachs'¹ case, and Russell's⁴ Case 2) no objective disturbance of the 5th nerve sensory function could be found; and in 2 others (Cases 1 and 3, of this communication) the only objective disturbances of the trigeminal functions were, respectively, some hypesthesia in the area of a previous peripheral nerve avulsion, in Case 1, and hyperesthesia in the trigeminal area in Case 3. The author has had the privilege of reviewing the history and of examining the sections of the ganglion of another case reported by Carnett²¹ in which there were metastatic carcinomatous deposits scattered widely throughout the bones and the organs, one deposit having invaded the left ganglion. Although there were definite nests of carcinomatous cells in the ganglion itself, the only objective clinical findings which might have been dependent upon such a lesion were a decrease in size of the left pupil as compared to the right and a tenderness of the scalp and face to pressure. The only suggestive symptoms in the history were headache and the statement of the patient that food did not taste good to him. That distinct objective changes had not occurred in these cases is remarkable when it is noted that at the time of observation symptoms had been present in Russell's Case 2 for 17 months, in Sachs' case for 10 months, in the author's Case 1 for 13 months, and in Case 3 for 7 months.

These exceptional cases have been mentioned particularly in order to illustrate the difficulties encountered in arriving at a diagnosis in some instances. Of the 22 case reports analyzed, the majority were sufficiently clear-cut to justify a positive diagnosis, and in these latter no essential variations from the usual clinical picture were encountered. With the exception of the cases particularly mentioned above, some impairment of the sensory or motor functions or of the reflex arcs dependent upon the integrity of the trigeminal pathways had given the clue pointing toward a destructive lesion of these pathways.

So far as the manifestations relating to the Gasserian ganglion *per se* are concerned, therefore, the clinical picture as formulated on the basis of the available reports of recent date most frequently is characterized either by an initial symptom such as pain in some part of the trigeminal distribution, subjective numbness in that area, impairment of vision or hearing, nausea, vertigo, or headache; or by an objective finding such as trigeminal sensory impairment or hyperesthesia, diminution of the corneal reflex, or weakness of the motor division; or by a combination of more than one of these

manifestations. It should be emphasized again, however, that occasional cases apparently have had no subjective symptoms pointing to the ganglion, and that a few others have showed no definite objective evidence of disease of the ganglion or the motor division. In conformity with the views of former writers, this study indicates that in the clinical course of ganglion tumors other cranial nerves on the side of the lesion, particularly the nerves to the ocular muscles, the 8th, the 7th, the 9th and 10th, and the 12th, in that order of frequency, may be affected.

The value of roentgenology in diagnosis does not appear to be dependable. Partial destruction of the sella turcica or erosion of the base of the skull were noted in 3 of the analyzed cases, but the changes were not distinctive of ganglion tumor. In the author's Case 3, the encephalogram was suggestive but not conclusive.

Syndromes closely resembling the clinical picture of tumor of the Gasserian ganglion may occur in association with tic douloureux, neuralgias secondary to sinus or dental disease, atypical neuralgia, postzoster neuralgia, syphilis, tuberculosis and cerebellopontile angle tumor. For discussions of these conditions and the helpful differential points, the reader is referred to the communications of Parker,³ Frazier,^{12,22} Cushing,¹³ Mixter and White,²³ Potts,²⁴ Cadwalader,^{15,25} Spiller and Camp,²⁶ and Spiller and Potts.²⁷ That cerebellopontile angle tumor occasionally may produce a symptom complex indistinguishable from that caused by a tumor primary in the Gasserian ganglion has been demonstrated in the experiences of Weisenburg,²⁸ Parker,²⁹ Oppenheim,³⁰ of Krause and of Lexer (quoted by Cushing¹³).

Contemporary opinion as to the pathology of tumors arising in the region of the ganglion varies to such an extent that the question cannot be considered in detail here. Spiller's¹⁴ warning of many years ago against the rigid classification and differentiation of such tumors on the basis of the interpretations of different observers applies today. The degree of malignancy of the tumors in this region, whether they be primary or metastatic, obviously influences the prognosis. However, a more definite and clear-cut microscopic classification, as well as further data on the clinical course of patients in whom these tumors are demonstrated is necessary before different plans of treatment dependent upon the pathology can be formulated. The pathologic diagnoses reported by the authors in the 22 cases analyzed for this communication were as follows: Endotheliomas, 10; neuromas, 2; sheath neuromas, 2; neurocytoma, 1; neurofibrosarcoma, 1; sarcoma, 1; fibroblastoma, 1; chondroma, 1; neurofibroma, 1; undetermined, 2.

Although surgical treatment of tumors of the Gasserian ganglion has been practised since the time of Krogus's³¹ first operation on such a case, the results of surgical treatment had not been encouraging until the time of Frazier's¹² case. Of the cases which the author has reviewed, 17 had been subjected to operations for removal of

the tumor or section of the sensory root of the trigeminus, decompressive operations had been done on 2 others and apparently an exploratory operation on a 3d case. Postoperative relief of pain resulted in 12 of the operated cases, the degree of relief and of permanence of relief varying considerably. Of the operated cases in which follow-up notes were mentioned and in which partial or total extirpation of the tumor or section of the sensory root had been done, the average period of known relief was 4.7 months and the average known duration of life after operation was 7.5 months. These averages are conservative, as 7 of the patients were living when last heard from, the periods of relief or the duration of life in these cases being counted as corresponding with the interval between operation and the date of the last follow-up note. The return of spontaneous pain after surgical extirpation of the tumor and division of the sensory root may be accounted for by recurrence of the tumor or invasion of the posterior fossa, as in Case 1. Following operation, irradiation is given and has been of value, as illustrated by the results in Rand's⁵ case.

The effect of operation upon the duration of life cannot be determined until larger groups of operated cases have been studied. However, it may be pointed out that in this series of 20 operated cases, death attributable to operation occurred only 2 times, the operation having been done for the purpose of decompression in 1 of these cases and for exploration in the other.

Sachs'¹ recommendation that operation be performed on patients having severe continuous pain in the trigeminal distribution, in the absence of sinus disease, without awaiting involvement of the motor branch of the trigeminus, appears to be justified by the results of surgical treatment in this group of cases. Furthermore, it may be pointed out that a ganglion tumor occasionally may be present for a considerable time without giving rise to any of the usual objective signs. In view of these facts, and in the light of Frazier's³² low operative mortality of 0.26 per cent from the middle fossa operation for trigeminal neuralgia, the justification for early middle fossa exploration by a competent operator for patients suffering unexplained constant trigeminal pain, with or without typical objective manifestations, does not appear to be strained. The relief of pain alone by section of the sensory root in otherwise inoperable cases, as previously suggested by Frazier,³³ may make the middle fossa operation worth while for such cases.

Summary. Three cases of tumor primary in the region of the Gasserian ganglion are reported. A review of 19 additional cases in the literature is summarized to illustrate the frequency of occurrence of the various initial symptoms and of the objective manifestations, and the results of operation in such cases. The difficulties of diagnosis in some instances are pointed out. The principal conditions which are to be differentiated from tumor and occasional indistinguishable conditions are mentioned. Attention is directed

to the gratifying results in a few cases subjected to early operation; to the relatively low operative mortality in excision of early lesions and in the less hazardous procedure of section of the sensory root; and to the possibility of symptomatic relief by division of the sensory root in cases of inoperable tumor.

Conclusions. 1. The clinical diagnosis of tumor of the Gasserian ganglion is not always possible in the light of our present knowledge, even when definite neoplastic involvement of the ganglion has occurred.

2. Occasionally such conditions as tic douloureux, atypical neuralgia, postzoster neuralgia, syphilis, and rarely tuberculosis and angle tumor may produce a clinical picture which cannot be distinguished from early tumor of the Gasserian ganglion.

3. Exploratory operation in the region of the Gasserian ganglion by competent operators is justified for patients who suffer suspicious constant trigeminal pain not satisfactorily explained, and for patients who show objective indications of interruptions of the trigeminal motor or sensory pathways without evidence of an etiology other than ganglion tumor.

4. Palliative section of the sensory root is justified in patients in whom extirpation of the tumor is not feasible.

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PNEUMONIA IN KEROSENE POISONING.

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THE toxic properties of kerosene are generally recognized, but the way in which the oil exerts its harmful effect in cases of serious or fatal poisoning is not clearly stated in the literature. Among the 23 cases admitted to the Roper Hospital in the past few years there have been a number of severe manifestations and 2 deaths. Many other children have been treated in the emergency room and allowed to return home because their symptoms were slight. Cases seem to be more common than previously and, because of the probability of the occurrence of serious intoxications in the future, the recent cases have been reviewed and certain experiments undertaken in an attempt to clarify the subject.

In the children made ill by kerosene the chief signs have been marked drowsiness or actual coma, fever and abdominal tenseness. Cyanosis and convulsions have been present in 2, vomiting and diarrhea in 2, and acetoneuria in 7 instances. Nine children have developed definite signs of pulmonary involvement varying from mild bronchitis to severe and fatal pneumonia.

The more noteworthy cases were as follows:

Clinical Notes. CASE 1.—Colored, male, aged 1 year. Drank a "small amount" of kerosene, and about $1\frac{1}{2}$ hours later became comatose, whereupon he was brought to the hospital and given a gastric lavage. Fine and coarse râles were heard over both lungs and dullness was found over the bases. A roentgenogram showed clouding of nearly the whole of the left lung and of an area in the right base. In spite of supportive treatment, after rousing somewhat, this child lapsed into coma and died about 11 hours after the ingestion of the kerosene (Fig. 1).

CASE 2.—Colored, female, aged 14 months. Swallowed about half a glass of kerosene and had gastric lavage within about 20 minutes. She was coughing, comatose and cyanotic, had contracted pupils, coarse râles over both lungs and showed a fine, almost constant generalized twitching. A colonic irrigation yielded fluid with a strong odor of kerosene. A roentgenogram made $3\frac{1}{2}$ hours after the kerosene was taken showed areas of increased density over both lungs along the course of the larger bronchi. Death occurred about an hour later.

CASE 3.—White, female, aged 3 years. Drank an undetermined amount of kerosene and almost immediately choked, became cyanotic and rapidly became drowsy. Gastric lavage was done within 20 minutes. Coarse râles were heard over both lungs, and a roentgenogram showed bilateral mottling. Later in the day high pitched breath sounds and crackling râles were heard in the left base. Next day the signs were less marked, although the roentgenogram showed practically the same picture. Three days later the lungs were clear clinically, and uneventful recovery followed. The edge of this

child's liver was 3 cm. below the costal margin, but no connection between this enlargement and the current illness was found.

CASE 4.—Colored, male, aged 2 years. Drank kerosene and was given castor oil and salts before he became comatose. His stomach was washed after about $2\frac{1}{2}$ hours. Râles, dullness and tubular breathing were found at the angle of the left scapula, and a roentgenogram showed clouding of the left lower lobe. Six days later the picture showed less density. After 8 days dullness was still present, but the child was so much improved that he was discharged (Fig. 3). A roentgenogram taken 8 months afterward was negative.

CASE 5.—White, male, aged 2 years. Took "three swallows" of kerosene, cried, flushed, coughed and soon became drowsy. His stomach was washed in about 2 hours' time. Occasional coarse râles were heard over both bases; the roentgenogram was negative. By the following day he was ready for discharge.

CASE 6.—White, female, aged 2 years. Drank kerosene, but was not seen at the hospital until 2 days later, when she showed râles and diminished resonance on both sides, and a tense abdomen. Recovery followed in 7 days.

CASE 7.—White, female, aged 2 years. Drank kerosene. Seen 5 days later and had cough, fever, pain in chest and a few râles. Three days later she seemed entirely well.

CASE 8.—White, female, aged 32 months. Drank about 3 ounces of kerosene. Developed no marked symptoms. Recovered.

CASE 9.—Colored, male, aged 3 years. Drank a half glass of kerosene. Had gastric lavage within a half hour. He developed a temperature of 104° F. and showed râles over both bases and roentgenologic evidence of congestion in those areas. He recovered in 24 hours.

CASE 10.—Colored, male, aged 14 months. Had gastric lavage 10 minutes after drinking kerosene. He showed râles in both bases, and the roentgenogram showed clouding in the lower half of both lungs. Three days later the râles had disappeared, but the film was essentially the same. This child did not appear very ill and seemed well within 24 hours after the onset. The stool showed no blood.

The laboratory findings were not particularly significant. An increased total leukocyte count and polymorphonuclear percentage were usual. Methemoglobin was not demonstrated in the 4 cases in which tests were made. The cholesterol content of the blood was apparently reduced.

Usually the respiration was rapid, going as high as 140 in Case 1. The pulse rates were likewise high. In Case 3 the rectal temperature reached 104.6° F., in Case 9 it reached 104° F., and in Case 10 it went to 102.6° F., but did not exceed 102° F. in the others, and was of short duration as a rule. Cyanosis did not persist in the children who recovered.

In an effort to discover characteristic changes caused by kerosene, a few experiments with dogs were made. The clinical changes produced were quite similar to those found in the children.

Animal Experiments. DOG 1 (Weight, 14 kg.).—Was given morphin sulphate, $\frac{1}{4}$ gr. and atropin sulphate, $\frac{1}{10}$ gr., at 9.50 A.M. At 10.30 A.M. blood was taken for examination and 10 minutes later 250 cc. kerosene were given by stomach tube. At 11 A.M. the dog was drowsy. Rectal temperature at that time was 38° C., at 5 P.M. it was 40° C., and at 8 P.M., 38° C. The



FIG. 1.—Case 1. Lungs 3 hours after kerosene was taken.

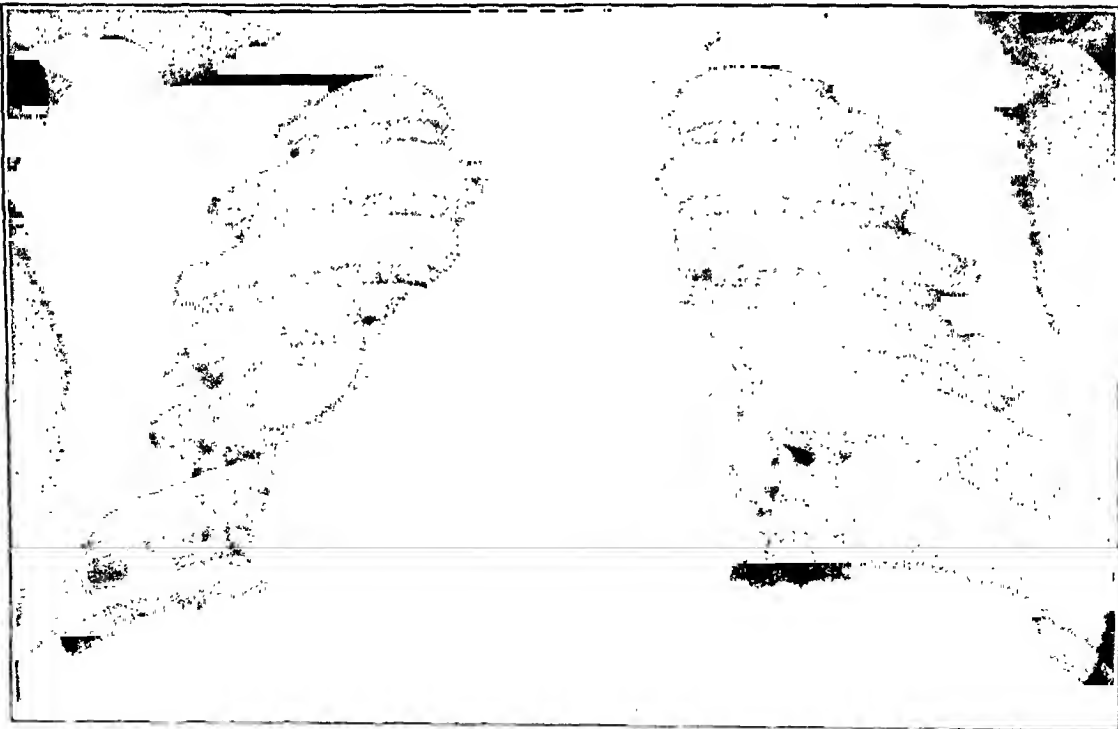


FIG. 2.—Case 3. Lungs $3\frac{1}{2}$ hours after kerosene was taken.

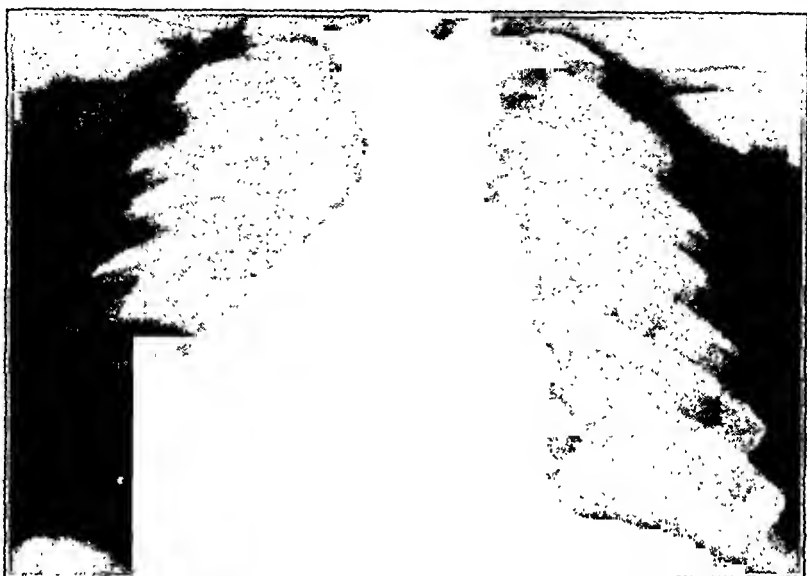


FIG. 3.—Case 4. Lungs about 5 hours after kerosene was taken.



FIG. 4.—Lungs of dog after intratracheal injection of kerosene. (Experiment IV.)

dog showed no other signs of intoxication and next day appeared well. Kerosene was passed per rectum on this second day. A roentgenogram of the chest 23 hours after kerosene was given was negative. A second sample of blood was taken 2½ hours after the first bleeding.

TABLE 1.—RESULTS OF BLOOD EXAMINATIONS.

	Before kero- sene.	2 hrs. after kerosene.		Before kero- sene.	2 hrs. after kerosene.
Hemoglobin (Dare)	80	78	R. B. C. (millions)	5.5	5.5
Sugar	65.8	63.9	Leukocytes	9700	12,500
Urea	7.8	8.3	Lymphocytes	33	26
Chlorids	546	528	Polymorphonuclears	62	71
Creatinin	1.3	1.0	Mononuclears	1	2
Cholesterol	54.7	44.0	Basophils	2	0
CO ₂	64	56	Eosinophils	2	1

These figures parallel the findings in the children, showing a moderate increase in leukocytes, polymorphonuclear percentage and a lowering of the cholesterol value.

Dog 2 (Weight, 6 kg.).—After administration of morphin and atropin was given 100 cc. of kerosene by stomach tube. Three hours later he was drowsy and his pupils were dilated, but otherwise showed no ill effects. Carbon dioxid combining-power was 57 before the kerosene was given, and 62 after 3 hours.

Dog 3.—Was given 100 cc. of kerosene by stomach tube. He vomited about 35 cc. Hemoglobin before administration was 105, and 2½ hours later was the same.

Dog 4.—A bitch, weighing 4.7 kg., showed a negative roentgenogram of the chest. Under light ether anesthesia 5 cc. of kerosene were injected into the larynx with the aid of a laryngoscope. Almost immediately there were convulsive twitchings of the body. One-half hour later the respiration was 180, rectal temperature, 39° C. After an hour, except for rapid respiration, the animal seemed to be recovering well. A roentgenogram showed a heavy shadow in the right lower lobe. After 24 hours the shadow in the right lower lobe was still present. The animal recovered uneventfully.

The similarity between the shadow in Case 4 and in the injected animal may be noted by comparison of the roentgenograms (Figs. 3 and 4).

Dog 5 (Weight, 12 kg.).—Was given 200 cc. of kerosene by tube. Through error the tube entered the larynx, as shown later at autopsy by the presence of a large amount of kerosene in the lungs. The effect was immediate; the dog developed marked extensor rigidity with opisthotonos, urinated, vomited (or coughed out) a few cubic centimeters of kerosene, rapidly became comatose, with Cheyne-Stokes respiration, and died in 45 minutes. The rapid development of symptoms in Case 2 suggests that the child might have aspirated a large amount of kerosene and followed a course similar to that produced by the rapid entrance of kerosene into the lungs of the dog.

Dog 6 (Weight, 14.85 kg.).—Without preliminary anesthesia he had 10 cc. of kerosene injected into the trachea through the neck at 9 P.M. At 9.15 P.M. he showed marked dyspnea and ataxia. At 9.25 P.M. he was unable to stand, and very dyspneic. His rectal temperature fell from 38° to 37.5° C. Respiration was 116 per minute. At 9.40 he was very drowsy, with irregular respiration, but could be roused. At 12 P.M. his temperature had dropped to 35.5° C., respiration to 64. He died between 1 A.M. and 8 A.M.

Autopsy showed both lungs congested, with excess of fluid, and consolidation of the left lower lobe and relative consolidation in the right lower and parts of the left upper. Microscopically capillary engorgement and heavy edema were present. In the more solidified parts the alveoli were

filled with fibrin and fluid, with large infiltration by small cells, some polymorphonuclears, but most of the lymphocyte type, obscuring alveolar walls and more or less filling alveoli and small bronchioles.*

TABLE 2.—BLOOD FINDINGS IN 10 CASES OF KEROSENE POISONING.

Case.	Leukocytes (thousands).	Lymphocytes.	Polymorpho- nuclears.	Monocytes.	Basophils.	Eosinophils.	Hemoglobin (per cent).	Sugar (mg. per 100 cc.).	Urea.	Creatinin.	Blood chlorida.	CO ₂ .	Cholesterol.	Methemoglobin.
1	19.3	24	72	2	1	1	70	66	0
2	18.4	30	65	1	0	4	70	126	11.3	1.3	...	64	47.6	0
3	13.5	46	51	1	0	2	68	105	8.9	1	511	66	41.2	0
4	10.1	25	69	4	0	2	..	118	17	50		
5	11.1	19	81	0	0	0	70	84	10	...	396	69		
6	23.4	26	68.5	3	1.5	1								
7														
8	18.5	27	72	1	0	0	85	67	9.5	1.2	475	82	64.5	0
9	11.1	35	54	6	0	5	60							
10	12.5	39	57	3	0	1	75							

TABLE 3.—URINE IN 10 CASES OF KEROSENE POISONING.

Case.	Reaction.	Albumin.	Sugar.	Acetone.	Casts.	Pus.	Blood.
1	Acid	++	0	0	0	0	0
2							
3	Alk.	+	0	Trace	0	+	0
4	Acid	0	0	0	0	0	0
5	Acid	0	0	0	0	0	0
6	Acid	0	0	++	0	0	0
7							
8	Acid	+	0	0	0	++	0
9	Acid	0	0	0	0	0	0
10	Alk.	0	+	++	0	0	+

Dog 7 (Weight, 6.15 kg.).—Had 7 cc. of kerosene injected into his trachea. He developed symptoms very similar to those noted in the last experiment, and died within 2 hours. *Autopsy*: Congestion, edema, hemorrhage. Early pneumonia, cellular exudation—not prominent as in other dog and proportionately more polymorphonuclears. Kidney: granular swelling of epithelium of convoluted tubules; fragmentation, granularity, vacuolization of epithelium of Henle's loop and collecting tubules. Liver: cells of central lobular zones quite granular. Trachea: minor desquamation of epithelium, a submucosal hemorrhage. Lungs: vascular engorgement, alveoli practically filled with blood, hyalin coagulum and cells, predominantly lymphocytes, next in prominence mononuclears, but a goodly proportion of neutrophils; small areas of necrosis here and there, with leukocytic accumulation.*

* Autopsy by Dr. K. M. Lynch. A more detailed report of the pathologic findings will be made in another article.

Discussion. The scanty literature relating to kerosene poisoning has little to say regarding the pulmonary complications, and deals mostly with gastrointestinal irritation. The toxic effect of inhalation of the vapor is recognized,^{1,2} but no stress is put on the likelihood of aspiration of the oil into the lungs, and the consequent rapid damage to the lung tissue. According to reports, the dose required for poisonous action seems to vary considerably with individuals, and the time for development of coma or serious symptoms likewise appears to be variable. Recovery of an adult after drinking $\frac{3}{4}$ liter is reported,³ while a child aged 18 months succumbed to 2 ounces.⁴ Death from bronchopneumonia occurred in an infant aged 6 months, into whose mouth an ounce of "petrol" had been poured $1\frac{1}{4}$ hours before.³ (Gasoline and kerosene are similar in general composition and effect, except that kerosene is said to be the more reactive.⁵) Seven fatal cases in children are found in detail in the literature.^{3,4,6,7,8}

Administration of petrol by stomach tube to rabbits is said by Le Gludie and Turlais³ to produce pulmonary congestion and punctate hemorrhage. These observers found that as much as 20 cc. per kg. was necessary for toxic effect on the rabbit, and were able to produce only gastrointestinal irritation in dogs.

The development of areas of pneumonic consolidation following the administration of oils by the nose or throat has been demonstrated by Laughlin.⁹ Pinkerton¹⁰ also has pointed out the fact that mineral oil evokes a tremendous cellular reaction in the lung, that it is easily emulsified and taken up rapidly by phagocytic cells. He furthermore notes¹¹ that aspiration of regurgitated stomach contents is not uncommon, and that spasm of the cardia may allow fluid to well back in the esophagus and spill over into the larynx. The type of oil seems to be important in the production of changes in the lungs, for lipiodol (iodized poppy-seed oil) does not cause pneumonia in dogs¹² and is given to human beings apparently without ill effect.

With these considerations in mind, and in view of the clinical and experimental findings, it would seem likely that the pulmonary complications of kerosene poisoning are due to aspiration of some of the kerosene directly into the lungs, or the aspiration of regurgitated kerosene from the stomach, and that the serious and fatal intoxications with this substance are due to the development of pulmonary inflammation with edema and, perhaps, to rapid absorption of the oil from the lungs.

Treatment. The results of treatment are not the most satisfactory. Supportive measures, especially stimulation with caffeine, have been used. Colonic irrigations and gastric lavage have been given, but if regurgitation is to be avoided, the use of lavage might be questioned. In 2 cases which recovered, postural drainage was instituted but no direct evidence of its efficacy was noted. The blood

chemical studies have not indicated any line of treatment. Because some of the children showed acetone in the urine, glucose has been given to the cases seen recently.

Summary. Nine cases of kerosene poisoning with pulmonary complications are reported. Leukocytosis with an increased polymorphonuclear percentage has been characteristic. The blood cholesterol appears to be reduced, but no other chemical change is noted. Animal experiments tend to confirm the clinical opinion that the serious and fatal cases of kerosene poisoning are due to the aspiration of kerosene into the lungs, with production of inflammation and edema, and a potentially fatal pneumonitis.

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THE EFFECT OF CEMENT DUST UPON WORKERS.*

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THE greater part of the material presented in this paper was gathered from experience met with in assisting in a study of workers who were exposed to varying concentrations of cement dust and from the report of this study, which includes analyses of all the data obtained from dust counts, chemical and petrographic analyses of the dust, morbidity records, and general physical examinations.¹ The purpose of the study was primarily to measure in terms of physical condition and disabling sickness the effects upon the

* Read before the Sixth International Congress on Industrial Diseases in Geneva, August, 1931.

workers of exposure to known quantities of dusts. The study was conducted in a plant which was selected because, in the first place, it appeared to be dusty enough to afford observation of the effect upon health of exposure to large amounts of calcium dusts (regarded by many as possessing properties beneficial to health) and of silica (known to be harmful in its free, crystalline state), and in the second place, the managers of the plant offered to cooperate and assist in the collection of data needed for such a study.

The importance of knowing the effect of cement dust upon workers is obvious, since there are in the United States at least 150 cement manufacturing plants in operation at the present time, employing over 42,000 workers, and a still larger number of persons will be required in the future to meet the increasing demands for cement in road making and building construction and the many new uses to which this product will be applied.

The study was conducted throughout a period of nearly 3 years, and the greater number of the workers underwent two general physical examinations. In addition to the general examinations, persons suspected of having chronic respiratory disease were given special chest examinations, in order to make possible more definite diagnoses. Roentgen-ray films were taken of the chests of employees in different occupations of the industry. The number of dust particles per cubic foot of air was determined for the different parts of the plant where the employees worked. The dust was examined chemically and petrographically. A record was kept also of all absences from work, and those lasting 2 days or longer were investigated by a nurse in the employ of the cement company. If the absence was found to be due to illness, a diagnosis was obtained, if possible, from the attending physician; otherwise, from the symptoms described by the patient.

The manufacturing of American Portland cement requires the mixture of limestone or marl with clay or shale, which are usually obtained by steam-shovelling in open quarries and subsequent crushing by machinery—processes which require little manual labor and hence the number thereby exposed to dust is small. These minerals are mixed in proper proportions and are pulverized by machinery to a fineness of 90 to 95 per cent, passing a No. 100 mesh screen. They constitute the "raw" material prepared outside the plant proper and conveyed automatically into the mill. The dust counts in the crushing and mixing rooms in a plant studied by us are given in Table 2.

The chief constituents of the dust in the crusher houses of the quarry are calcium carbonate, silica, and silicates. The quarry dust is practically 100 per cent inorganic material and contains moisture in amounts which vary in proportion to the amount of moisture in the outdoor air. The proportion of free silica (in the form of quartz) in samples taken from the crusher house, the raw

mill, and the stone house was found to be about the same (by petrographic analysis)—namely, 6.5 per cent.

The next step in manufacturing requires that this raw cement shall be burned at temperatures of from 1400 to 1600° C. It is then cooled, and a small percentage of gypsum is added. The mixture is then pulverized to such a fineness that at least 92 per cent passes through a No. 100 sieve and 75 per cent through a No. 200 sieve. It is then conveyed to storage for packing and shipment.

Exposure. The dustier occupations involve exposure to dust containing from 1 million to 105 million particles under 10 micra in the longest dimension per cubic foot of air. In the least dusty place the exposure varied from 400,000 to several million dust particles per cubic foot of air. Variations in amount of dust at the same place at different times were wide, depending in great measure on the direction and velocity of the wind and certain other factors.

Chemical analysis showed that lime constituted about 60 per cent of the cement manufactured in the plant under study, and silica about 20 per cent. Iron and aluminum oxides, magnesium oxid, and calcium sulphate were some of the other more important constituents of the cement.

TABLE 1.—CHEMICAL COMPOSITION OF DUST BREATHED BY EMPLOYEES IN SPECIFIED DEPARTMENTS OF A CEMENT PLANT.*

Constituents calculated as follows:	Crusher houses, %.	Stone house, %.	Raw mill, %.	Kiln room, %.	Finishing mill, %.	Bag house, %.	Packing house, %.
Silica (SiO ₂)	15.70	17.80	17.00	15.00	18.00	21.30	21.20
Iron and aluminum oxides (R ₂ O ₃)†	6.20	9.10	7.10	4.20	7.30	7.50	8.40
Lime (calcium oxid) (CaO)	41.93	36.11	37.71	38.11	60.18	54.56	60.88
Magnesium oxid (MgO)	2.64	2.46	2.17	2.06	2.61	2.68	2.97
Calcium sulphate (expressed as SO ₃)	4.08	2.18	1.75
Loss on ignition (carbon dioxide, water, organic matter)	33.45	34.30	36.02	40.40	7.90	11.70	4.75
Totals	99.92	99.77	100.00	99.77	100.07	99.92	99.95

* The chemical analysis of dust in the coal house was as follows: volatile combustible matter (sulphur, 2.51 per cent), 27.05 per cent; fixed carbon, 46.85 per cent; ash, 26.1 per cent.

† The symbol R stands for both iron and aluminum, since these two oxides were determined as a whole.

Petrographic analysis showed that the proportion of uncombined silica (in the form of quartz) was about 6.5 per cent in all departments before the cement was burned in the kilns. The burning of the raw cement in the kilns produced chemical changes, so that much of the free silica combined with the various chemical elements

in the raw material to form silicates, leaving only about 1 per cent of free silica (quartz) in the finished cement.

The chemical analysis of the finished product has been given above; the petrographic analysis of a sample of cement dust taken from the air of the packing house was found to contain no recognizable grains of calcium carbonate or any claylike material, but appeared to contain about 1 per cent of quartz grains. The dust in the packing house is similar in nature to that found in the departments following the kiln rooms. The finished cement apparently contains, therefore, about 1 per cent of silica in the free state.

From the foregoing statements, it is apparent that the worker in a cement mill is exposed to free crystalline silica, or quartz, in percentages indicated below:

TABLE 2.

		Number of particles per cubic foot.	Free silica, per cent.
Raw cement	Quarry	2,485,000	6.5
	Raw mix room	19,861,000	
	Raw mill	92,035,875	
Finished cement	Kiln room	8 to 20 million	1.0
	Finishing mills	8 to 62 "	
	Bag house	18 to 32 "	
	Packing house	19 to 40 "	

Disabling Sickness. Sickness rates for specific diseases causing disability among the men on the factory payroll of a rubber company in the State of Massachusetts were available for comparison with the experience of the cement workers. (The cement plant where this study was made is located in the middle Atlantic section where the climate is much milder than that of Massachusetts.) The diseases which occurred more frequently in the cement workers than in the rubber workers were in the order of the magnitude of the excess in disability among the former: (1) bronchitis; (2) diseases of the skin; (3) influenza; (4) diseases of the eyes and ears; (5) diseases of the pharynx and tonsils; (6) rheumatism; (7) diseases of the digestive system; (8) diseases of the nasal fossæ. Respiratory diseases other than those named above occurred at a relatively low rate among the cement workers.

Only 3 cases of pneumonia and only 1 disability from tuberculosis appear to have occurred in an exposure of 763 years of life. The age distribution in both these companies was practically the same, and other factors varied but little. The respiratory problem in this cement plant and probably in others showing similar dust concentrations is apparently confined to diseases of the nasal fossæ, acute bronchitis, and diseases of the pharynx and tonsils, with influenza, or grippe.

Seventy per cent of the diseases of the skin were due to furunculosis. Most of these occurred during the summer months and in

workers in the finishing mill and were caused, no doubt, by the clogging of the sebaceous glands with cement dust and by subsequent infection.

TABLE 3.—COMPARATIVE FREQUENCY OF SPECIFIED DISABILITIES AMONG A GROUP OF CEMENT WORKERS AND AMONG MEN ON THE FACTORY PAYROLL OF A RUBBER COMPANY IN MASSACHUSETTS.*

Diseases causing disability.†	Annual number of absences per 1000.		Ratio to rate for rubber workers.‡	No. of absences.	
	Cement workers.	Rubber workers.		Cement workers.	Rubber workers.
Total disability§	725	318	228	553	3857
1. Bronchitis (99)	50	8	625	38	99
2. Diseases of the skin (151-154)	49	9	544	37	109
3. Influenza, or grippe (11)	206	63	327	157	770
4. Diseases of the eyes and ears (85), (86)	16	5	320	12	60
5. Diseases of the pharynx and tonsils (109)	75	25	300	57	301
6. Rheumatism, acute and chronic (51,52)	34	12	283	26	149
7. Diseases of the digestive system (108, 110-127)	114	46	248	87	555
8. Diseases of the nasal fossæ (97)	94	54	174	72	653
9. Other respiratory diseases (31, 98, 100-107)¶	10	12	83	8	143
Ill-defined and unknown diagnoses (205)	9	38	24	7	464
All other diseases and conditions¶	68	46	148	52	554

Years of life under observation: cement workers, 763; rubber workers, 12,147.

* In both groups only those absences were included which lasted two consecutive working days or longer. The record for the cement workers extended from February 6, 1922, to February 1, 1925; for the rubber workers, from January 1, 1922, to December 31, 1924.

† Title numbers in parentheses are taken from the International List of the Causes of Death, third revision, Paris, 1920.

‡ Sickness rates of the rubber workers = 100.

§ Exclusive of accidents and alcoholism.

¶ Includes 3 cases of pneumonia and 1 of pulmonary tuberculosis among the cement workers.

¶ There were only two infectious diseases among the cement workers; 1 case of measles and 1 of typhoid fever.

The greatest incidence of rheumatism occurred in the two outdoor departments of the plant, the yard and the quarry, and among men in the mechanical department. These groups were exposed to sudden changes of atmospheric conditions because of their environment. Obviously rheumatism is not associated with the dust problem.

Conjunctivitis was the most common affection of the eyes. During the physical examination it was found that the cars of many workers were plugged with cerumen and cement dust. This condition resulted in impaired hearing, but produced no actual disabling illness.

The digestive illnesses causing disability were for the most part confined to the summer months. The rates for such illnesses were higher among the men in the finishing and bagging departments than among those in other departments, perhaps because of the fact that workers in the finishing and bagging departments ingest larger amounts of the dust.

Pneumoconiosis. The extent of generalized fibrosis of the lungs among these workers was not sufficient to warrant a diagnosis of this disease, as such, by general physical examination. The cases diagnosed as having pneumoconiosis were found by means of the Roentgen ray. The fibrosis shown on the films was of a bilateral distribution and had also many of the other common characteristics of occupational fibrosis. The general nature of the films indicated that the involvement present was less extensive than that found in other cases from occupations which occasioned exposure to a greater percentage of free silica. There were no cases of disability from this cause, and the extent of the condition was not sufficient in any case to cause clinical symptoms. There were no cases of active tuberculosis found among those workers who had evidence (by Roentgen rays) of an occupational fibrosis. The Roentgen ray films of all the cement workers contained evidence of more calcifications than those in the series made on granite cutters. Granite contains very little calcium.

Pulmonary Tuberculosis. Particular attention was given to men who were found to have any chronic respiratory symptoms or signs; they were given closer observation and more detailed chest examinations, and it is believed that no cases of tuberculosis were missed. Suspected and positive cases of pulmonary tuberculosis totaled 21 among the 570 examined, and in only 2 of these 21 cases were there signs of active disease. In a greater portion there were fibrosis and other signs which were indicative of previous infection, though the disease did not at any time reach the stage where there was subjective clinical evidence of pulmonary tuberculosis. In other words, these cases were of the "closed" type. Regarding the 2 active cases which were found, it was evident from the histories and physical conditions that in these cases the disease had developed before service in the cement industry. One of them was of the chronic fibroid type, and the man knew that he had tuberculosis for many years. He died (near the age of 50 years) about a year after the study had closed. In the other case the man who was younger continued working, and the disease appeared to become quiescent.

The workers of the group which had positive signs of arrested tuberculosis were able to work in the dusty atmosphere without any apparent harm to their old tuberculous lesions. The dusts produced in manufacturing Portland cement in the plant under observation contained free silica in proportion varying from 1 to 6.5 per cent, according to the stage of the manufacturing process, and from

30 to 60 per cent of calcium oxid (lime). The amount of calcium in relation to silica or other constituents of inhaled dust appears to be of importance in the incidence and development of industrial tuberculosis. Two facts in this connection stand out prominently in the study: first, no new cases of tuberculosis were found to have appeared as the result of exposure to cement dust; and second, the cases which had unmistakable evidence of arrested tuberculosis exhibited no tendency to reactivation of the disease. We are led to believe that exposure to dust generated in the manufacture of Portland cement is not provocative of tuberculosis, nor is it a factor in reactivation of arrested disease. The following table is a summarization of the incidence of early pneumoconiosis and of this condition when complicated by tuberculosis. The tuberculosis was not active.

TABLE 4.—CEMENT WORKERS. RELATION OF YEARS OF EXPOSURE TO ROENTGENOGRAPHIC DIAGNOSIS.

	Years in cement.						Percent- age.
	Up to 5.	5 to 9.	10 to 14.	15 to 19.	20 to 24.	Total.	
Negative	3	1	1	1	..	6	11.3
More fibrosis than usual . .	14	7	1	22	41.5
More fibrosis than usual, with infection (tuberculosis) . .	7	1	1	1	..	10	18.9
Early pneumoconiosis . . .	4	4	3	11	20.8
Early pneumoconiosis, with infection (tuberculosis) . .	1	1	..	2	..	4	7.5
Total	29	14	6	4	..	53	

We have shown² that workers can tolerate an exposure to a dust containing 35 per cent of quartz in a concentration of 10 to 20 million particles per cubic foot without having a tuberculosis rate greatly above that of the general population in the registration area of the United States. It is not reasonably to be supposed that cement workers would develop silicosis to any great extent, since the highest silica content in cement dust is only 6.5 per cent. Since they do not have marked silicosis, it is not surprising that they do not show excessive rates of tuberculosis. In the light of these facts we are still unable to state whether or not calcium possesses anti-silicotic properties. It is common knowledge that the presence of a latent or concurrent tuberculous infection will cause silicosis to develop more rapidly, and it is quite possible that certain mixtures of dusts may be capable of such effects or the opposite; but more information, both experimental and clinical, is needed to substantiate this theory. It would be a great aid in the amelioration of dust hazards if it were possible to render a harmful dust inert by mixing with it one which has been proved to possess antisilicotic

properties. Such an expedient would obviate the necessity for great expenditures in the installation and operation of ventilating equipment and would do away with the present-day use and abuse of masks.

Summary. In 1928 the cement industry employed about 42,000 men in about 150 manufacturing plants, representing an investment of more than \$500,000,000. The greatest concentration of dust was found at a mill where the average number of dust particles under 10 micra was 92 million particles per cubic foot of air. Other dusty locations showed counts which ranged from 22 million to 63 million particles per cubic foot of air. Variations in the dust count were found to depend to a great extent upon the direction and velocity of the wind and other atmospheric conditions.

Chemical analysis showed that lime constituted about 62 per cent of cement, and silica about 22 per cent. Alumina, iron oxid, magnesia, and sulphur trioxid are the other more important constituents of cement. Petrographic analysis showed that the proportion of free silica (quartz) varied from $6\frac{1}{2}$ per cent in the crusher houses, raw mill, and stone house to about 1 per cent in the finished cement.

The frequency of disability on account of respiratory diseases among the cement workers was twice as great as the average respiratory rate among employees of eleven manufacturing plants in relatively nondusty industries. The highest rate for all respiratory diseases in any of these establishments was 30 per cent below the rate of the cement workers.

Diseases of the skin gave a high rate of disability, and furunculosis (boils) was the cause of 70 per cent of the absences which were due to skin diseases.

The highest incidence of rheumatism occurred in the outdoor workers and there was a seasonal variation of the disease.

Conjunctivitis was the most frequent disability of the eyes.

The men employed in the finishing, bagging and packing departments had a rate almost twice as high as for those in the other departments for gastrointestinal disturbances. There was a marked seasonal variation for this condition.

There was a seasonal variation in respiratory diseases, which would be expected; the peak was reached in February. The respiratory rate varied more in accordance with general physical condition than with age.

Of the 570 workers examined, 21 (3.7 per cent) were diagnosed as having either positive or suspected pulmonary tuberculosis. In only 2 cases, however, was the disease active at the time of the first series of special chest examinations, and neither appeared to progress as a result of exposure to dusts. The history of both cases indicated that the disease had developed before their work in the cement industry. One of them gave a history of infection last-

ing many years, of chronic fibroid type, and he died suddenly about a year after cessation of the period of observation. The other became a quiescent case while working and during the progress of our study.

The other cases, excepting the suspects on whom we were unable to make a positive diagnosis of tuberculosis, seemed to have developed and healed their tuberculous lesions prior to exposure to cement dust, and there was no evidence that their lesions were reactivated during the period of their dust exposure.

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THE EFFECT OF IRRADIATED ERGOSTEROL ON CALCIFICATION OF TUBERCLES IN EXPERIMENTAL TUBERCULOSIS.

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THE value of vitamin D in stimulating calcification has been demonstrated in rickets and osteomalacia. The fact that calcification of tubercles plays an important part in the healing of tuberculosis has led to considerable investigation concerning the effect of irradiated ergosterol on tuberculous lesions.

Levaditi and Li¹ injected human tubercle bacilli into the testicles of rabbits and found that the oral administration of so-called "sub-toxic" doses (5 mg. per kilo) of irradiated ergosterol caused intense calcification of tubercles which had developed in the lungs and testicles. Calcium deposits were not found in the normal tissues. Spies² administered massive doses of irradiated ergosterol (viosterol) to rabbits in which both acute and chronic bovine tuberculosis had been produced by intravenous injection of a heavy suspension of avirulent tubercle bacilli. He noted marked calcification of the caseous tubercles in the lungs, liver and spleen. Later Walker and Spies³ obtained similar results in guinea pigs with acute bovine tuberculosis by feeding irradiated ergosterol. Policard, Ravault and Barral⁴ were able to produce calcium deposition in the caseated tubercles of guinea pigs with bovine tuberculosis, but they also noted deposition of calcium in normal organs. Simonnet and

Tanret⁵ showed, by chemical analysis, that irradiated ergosterol, when administered to normal and tuberculous rabbits, caused a rapid increase in the amount of calcareous salts in the lung tissue. This increase was approximately four times as great in the tuberculous rabbits as in the healthy animals. Loewy and Gruninger⁶ injected a culture of human tubercle bacilli subcutaneously into the abdominal wall of guinea pigs and studied the effect of administering irradiated ergosterol (vigantol) alone and in combination with calcium gluconate. Their results indicated that the animals had a diminished resistance to the disease when the vigantol and calcium gluconate injections were combined.

There are several factors which prevent a satisfactory evaluation of the foregoing reports. In the first place, much of the work was conducted on rabbits and it is well known that these animals show an anomalous susceptibility to the calcifying effect of both irradiated ergosterol and calcium salts. Preparations of irradiated ergosterol other than viosterol were employed in some instances and a number of the preparations were not biologically standardized. In addition, the various types and strains of tubercle bacilli may influence the lesions so that comparison of results is difficult. Recently, Spies⁷ was unable to produce calcification of tuberculous lesions in guinea pigs with experimental avian tuberculosis, using massive doses of viosterol.

Experimental. Two series of experiments (Series A and B) were conducted, employing for each series 13 guinea pigs, weighing about 325 gm. each. Series A (see table) was divided into Groups I, II, III and IV, and Series B into Groups V, VI, VII and VIII. One one-hundredth milligram of a known virulent culture of human tubercle bacilli (Strain H119)* was injected intramuscularly into the right groins of 10 of the 13 animals in Series A (Groups I, II and III). The remaining 3 guinea pigs in this series were not inoculated with tubercle bacilli and served as controls for the viosterol dosage (Group IV). In Series B an attempt was made to simulate tuberculosis as it occurs in human beings by producing secondary tuberculous lesions. Accordingly, a preliminary sensitizing injection of a known avirulent strain of human tubercle bacilli (0.1 mg. of Strain R1)† was given intramuscularly to each animal in the second series (Nos. 14 to 26) and, 6 weeks later, the virulent tubercle bacilli (H119) were injected into these animals. The experiment, as described for Series A, was duplicated in detail with Series B (see table) commencing 6 weeks after the animals received their preliminary sensitizing injections.

All animals were fed a normal laboratory diet to which 0.75 per cent of calcium carbonate was added. In addition to this food

* Furnished through the courtesy of Dr. Robert Bloch of the University of Chicago.

† Ibid.

TABLE 1.—RÉSUMÉ OF INVESTIGATION.

Group No.	Viosterol, 1000X (daily dosage).	Animal No.	Lymph nodes.		Spleen.		Liver.		Lungs.		Heart.		Aorta.		Kidneys.		Blood serum (mg. per 100 cc.).
			Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.	Lesions.	Calcif.			
SERIES A.																	
Injected intramuscularly with 100 mg. of virulent strain (H119) of human tubercle bacilli.																	
I	0.1 cc., 1st to 14th day 0.2 cc., 15th to 84th day	1	C.	++++	Tub. and C.	+++	Tub. and C.	+++	Tub.	+++	Nor.	+++	Nor.	++++	No tub. or C.	+++	12.9, 8.2
		2	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	12.2, 7.5
		3	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	11.7, 7.4
		4	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	..
II	No viosterol, 1st to 14th day 0.2 cc., 15th to 30th day 1.0 cc., 31st to 84th day (No. 8 died on 30th day)	5	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	13.6, 8.0
		6	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	13.0, 9.6
		7	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	..
		8	"	++++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	..
III	(Tuberculous controls) No viosterol	9	"	++	"	++	"	++	"	++	"	++	"	++	"	++	11.3, 5.3
		10	"	++	"	++	"	++	"	++	"	++	"	++	"	++	11.6, 5.1
IV	(Nontuberculous controls) 0.1 cc., 1st to 14th day 0.2 cc., 15th to 84th day (No. 12 died on 44th day) (No. 13 died on 61st day)	11	Nor.	++	Nor.	++	Nor.	++	Nor.	++	"	++	"	++	"	++	11.7, ..
		12	"	++	"	++	"	++	"	++	"	++	"	++	"	++	..
		13	"	++	"	++	"	++	"	++	"	++	"	++	"	++	..
SERIES B.																	
Preliminary sensitization with avirulent strain of human tubercle bacilli (R1)—10 mg. intramuscularly. After 6 weeks virulent strain (H119) injected as in Series A.																	
V	No viosterol, 1st to 44th day 0.1 cc., 45th to 60th day 0.2 cc., 61st to 84th day	14	Much C.	++++	Tub.; confl. C.	++++	Tub.; confl. C.	++++	Many tub.	++++	Nor.	++++	Nor.	++++	No tub. or C.	++++	11.3, 5.5
		15	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	11.8, 6.9
		16	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	11.6, 7.1
		17	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	..
VI	No viosterol, 1st to 60th day 0.2 cc., 61st to 70th day 1.0 cc., 71th to 84th day	18	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	C, rt. kidn. No tub. or C.	++++	9.4, 6.9
		19	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	..
		20	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	..
		21	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	"	++++	..
VII	(Tuberculous sensitized controls) No viosterol	22	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	10.4, 3.7
		23	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	"	+++	..
VIII	(Nontuberculous sensitized controls) No viosterol, 1st to 44th day 0.1 cc., 45th to 60th day 0.2 cc., 61st to 84th day	24	Nor.	++	Nor.	++	Nor.	++	Nor.	++	"	++	"	++	"	++	12.0, 7.7
		25	"	++	"	++	"	++	"	++	"	++	"	++	"	++	11.8, 8.0

+++++ = extensive; ++++ = marked; +++ = moderate; ++ = slight; + = trace; O = no calcification; C = caseation; Tub. = tubercles

+++++ = extensive; ++++ = marked; +++ = moderate; ++ = slight; + = traces; O = no calcification; C = caseation; Tub. = tubercles

mixture daily rations of carrots were given. The high calcium content in the food mixture was supplied in order to prevent bone demineralization. To check the calcium content of the bones, roentgenograms of all of the animals were taken at the beginning of the investigation and repeated at monthly intervals. The final Roentgen rays showed exactly the same bone density as the initial plates. Each of the 8 groups of animals was kept in a separate cage. The irradiated ergosterol used in this investigation was a special preparation (viosterol in oil 1000X)* possessing ten times the potency of viosterol in oil 250 D, and was administered by mouth with calibrated pipettes.

Each guinea pig in Group I (Nos. 1, 2, 3 and 4) was given daily 0.1 cc. of this preparation of irradiated ergosterol from the 1st to the 14th day, and 0.2 cc. from the 15th day until the completion of the experiment (85th day). Our aim in starting the administration of viosterol to this group before the development of tuberculous lesions was to note any possible prophylactic value.

The animals in Group II (Nos. 5, 6, 7 and 8) were given 0.2 cc. of viosterol daily from the 15th to the 30th day. On the 30th day animal No. 8 died during a period of extremely hot weather. The viscera of this animal, on postmortem examination, did not show any gross calcification of the tuberculous lesions. (Microscopic findings will be discussed later). Therefore, the viosterol dosage for the remaining 3 animals (Nos. 5, 6 and 7) in this group was increased to 1 cc. daily, which was continued from the 31st day until the end of the experiment. During this period the viosterol was omitted every 4th or 5th day.

Group III consisted of 2 tuberculous control animals (Nos. 9 and 10) which did not receive viosterol. Group IV included the 3 nontuberculous control animals (Nos. 11, 12 and 13). This group was given 0.1 cc. of viosterol daily for 14 days and 0.2 cc. of viosterol from the 15th day until the end of the experiment, the dosage being the same as in Group I. Two of these animals died of pneumonia, No. 12 at 6 weeks and No. 13 at 8 weeks.

In Series A the animals showed a steady gain in weight for 10 weeks, followed by a period of stationary weight or slight loss. The average total gain for each animal was 150 gm. The tuberculous animals in this series (Nos. 1 to 8) which received viosterol lost only 25 to 35 gm. during the last 2 weeks of the experiment. The animals in Series B gained steadily for 9 weeks, the average total gain being 200 gm. After the 9th week the animals in Groups V, VI and VII began to lose weight perceptibly. The 2 sensitized guinea pigs (Nos. 25 and 26) which were not inoculated with the virulent culture but were given viosterol, continued to gain weight until the end of the experiment. The experiment was ended on the

* Supplied through the courtesy of Mead Johnson & Co.

85th day when several animals in Series B began to lose weight rapidly.

In terminating the experiment each animal was given a lethal ether anesthetic and sufficient heart's blood was withdrawn during the anesthesia for serum calcium and phosphorus determinations.* Compared with an average blood calcium level of 11.6 mg. per cc. and an average phosphorus of 5.4 mg. obtained by making determinations on the blood of 30 normal guinea pigs, all animals in Groups I and II showed both hypercalcemia and hyperphosphatemia. The calcium values were from 1 to 2 mg., and phosphorus from 2 to 4 mg. above the average normal levels. No significant variations from the normal were found in the remaining animals except those in Group VIII (Nos. 25 and 26), the nontuberculous sensitized controls which were given viosterol. In this group the average calcium level was 11.9 mg. and the phosphorus 7.8 mg.

Necropsies were performed immediately after the death of the animals. Tissues for examination were taken from the lymph nodes (inguinal, iliac and tracheobronchial), spleen, liver, lungs, heart and aorta. They were fixed in 10 per cent formalin and imbedded in paraffin. In order to identify the calcium deposition, all sections were stained in duplicate, one set with hematoxylin and eosin and the other by the silver method of von Kossa. Calcium deposits could be identified by the hematoxylin and eosin stain as readily and clearly as with the von Kossa method.

On gross examination the animals in both series showed typical lesions of miliary and caseous tuberculosis involving the lymph nodes, spleen, liver and lungs. One kidney of animal No. 14 (Group V, Series B) presented a few small areas of caseation. Tuberculous renal lesions could not be found in any of the other animals. The lymph nodes were enlarged and showed extensive caseation in all animals except the nontuberculous controls. The heart and aorta of all of the animals appeared normal. Although typical tuberculous lesions were produced in both Series A and B, the sensitized group showed a more intense tuberculous involvement. The spleen and liver of the animals in Series B were markedly enlarged and contained large confluent areas of caseation. The cut surfaces of the spleen and liver of the inoculated animals in Series A which had received viosterol presented several hard, white, calcareous spicules, 1 to 2 mm. in diameter. Microscopic examination confirmed the gross findings.

In Series A a striking illustration of the calcifying effect of viosterol on tuberculous tissues was found. The tuberculous animals which did not receive viosterol (Group III) presented lesions with the same degree of tissue involvement as those to which viosterol

* Determinations were made in the Department of Chemistry. (Calcium by Clark-Collip modification of the Kramer-Tisdall method, and phosphorus by the Briggs modification of the Bell-Doisy method.)

was administered. Calcification was absent in this group (III). In Group I (Animals 1, 2, 3 and 4) calcification occurred in the lymph nodes and spleen of each animal. In addition, Animal 3 showed calcification of the central necrotic area of a few tubercles in the lungs (Fig. 1) and liver. One tubercle in the liver was completely calcified and particles of calcium could be detected in the necrotic areas of the other tubercles. Animal 4 showed a few small deposits of calcium in the walls of the bloodvessels and tubules of the kidney without any tuberculous lesions.

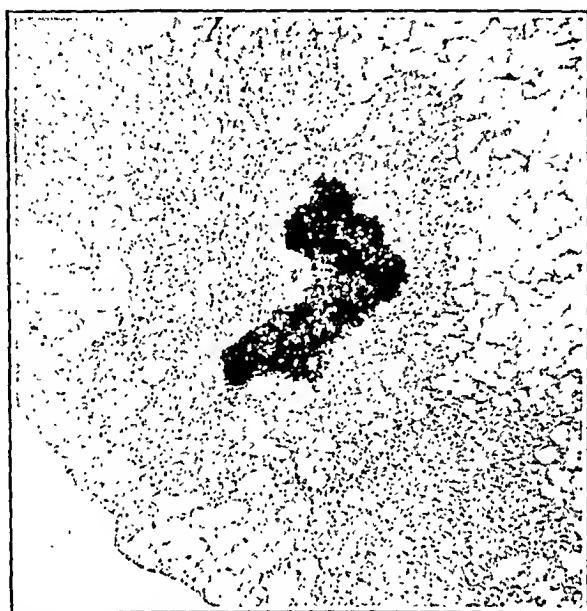


FIG. 1.—Section of lung. Hematoxylin and eosin stain. Magnification $\times 20$. Center of one tubercle shows marked calcium deposit (black area).

In Group II (Animals 5, 6 and 7), extensive calcium plaques were found in the lymph nodes. In some of the lymph nodes calcification occurred almost entirely at the periphery of the caseous areas, but a few calcium deposits were also noted in the centers of the necrotic areas. The spleen (Fig. 2) in each animal of this group showed marked calcification. Many tubercles were completely calcified, one being entirely surrounded by fibroblastic tissue. Moderate calcification occurred in the liver of Animal 5. There was an absence of calcification in the lungs of this group (II). Calcification of the walls of the renal bloodvessels and extensive deposits of calcium in the tubules of the kidneys occurred in each animal of this group. Spies and Glover³ reported similar renal lesions in normal rabbits with the administration of repeated massive doses of viosterol (3 to 10 cc. viosterol 1000X) at intervals of 1 to 4 days for a period of 60 days.

It was interesting to note a very slight calcification of the wall

of the renal arterioles in Animal 11, a nontuberculous guinea pig which received viosterol for the entire period of investigation. All other tissues of this animal were normal. The other 2 nontuberculous control animals (Nos. 12 and 13) of this group (IV) which died earlier in the experiment showed no calcification in the kidneys. These 2 animals had received viosterol for, respectively, $1\frac{1}{2}$ and 2 months at the time of their death. It would appear from these facts that the daily administration to guinea pigs of 0.2 cc. viosterol 1000X may be continued safely for at least 2 months, but less than 84 days. This daily dosage is equivalent to 6 cc. per kilo of viosterol 250 D.

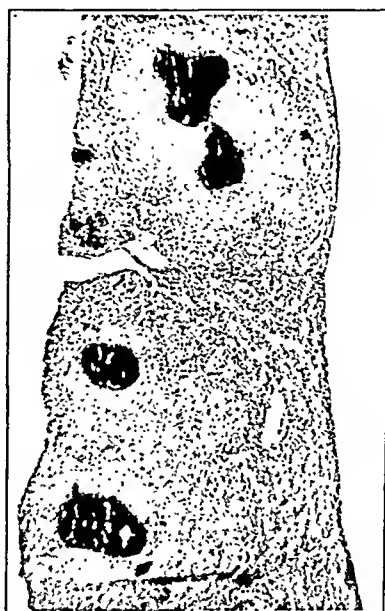


FIG. 2.—Section of spleen. Hematoxylin and eosin stain. Magnification $\times 20$. Marked calcification (black areas) of several tubercles.

In Series B, Group VIII (Nos. 25 and 26), the sensitized animals which did not receive a subsequent injection of virulent bacilli, presented normal tissues and no calcification. The microscopic sections of Series B, aside from this group, showed many typical tubercles and areas of caseation in the spleen and lungs of all the animals. The lymph nodes and liver presented extensive caseous areas. In the necrotic portions of the tubercles in the lungs of 3 animals in Group V, there were a few minute calcium-staining particles but no definite calcification. Calcification was absent in all other sections of Series B.

Summary. 1. In two series of experiments 10 guinea pigs were injected intramuscularly with a virulent culture of human tubercle bacilli, 3 serving as nontuberculous controls. In Series B an attempt

was made to simulate tuberculosis as it occurs in human beings. The procedure was the same as in Series A, except that a preliminary injection of a known avirulent strain of human tubercle bacilli was given to all 13 animals 6 weeks before the virulent culture was introduced. The effect of viosterol (administered orally) upon the lesions produced was investigated.

2. This demonstrated in a striking manner that the daily administration of viosterol in oil 1000X, in doses varying from 0.1 to 1 cc., causes deposition of calcium in the caseous tubercles in guinea pigs. The blood of the animals so affected showed both hypercalcemia and hyperphosphatemia. There was no evidence of calcium depletion in the roentgenograms of the bones.

3. Spontaneous calcification did not occur in the tuberculous animals which received no viosterol.

4. The most intense calcification was found in the lymph nodes and spleen of those tuberculous animals which were given the largest doses of viosterol. Calcium deposits were noted only in the caseated areas.

5. Undesirable calcification results if viosterol is given over a prolonged period in excessively large doses. In our investigation 0.2 cc. of viosterol in oil 1000X was administered daily for 2 months without any apparent harm. When continued for 84 days undesirable calcification occurred. This dosage is equivalent to 6 cc. per kilo of viosterol in oil 250D.

6. Calcification was present in the walls of the renal bloodvessels and in the renal tubules of both the tuberculous and nontuberculous animals which received daily amounts of viosterol in oil 1000X varying from 0.5 cc. to 1 cc. for more than 2 months. No calcium deposits were seen in the apparently normal portions of any of the other organs.

7. The tuberculous animals which received the preliminary sensitizing injection did not show any definite calcification, possibly because the effect of viosterol is diminished in the presence of a fulminating secondary tuberculous process.

8. The calcification of tubercles which was noted in this investigation is, in our opinion, not merely an expression of simple tissue necrosis but rather a reparative process. If it is permissible to calculate a human dosage of viosterol on a basis of weight, the maximum daily dosage given to our guinea pigs corresponds to a dosage of 300 cc. of viosterol in oil 250D, if given to a child weighing 22 pounds. We refrain from making any recommendation concerning the clinical application of viosterol in tuberculosis because of possible renal damage. Future research may determine an optimum dosage which may have clinical value in certain types or stages of the disease.

NOTE.—We are greatly indebted to Dr. Robert Bloch of the University of Chicago and Drs. Otto Saphir and David Cohen of the Michael Reese Hospital for their assistance and advice.

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THE EVOLUTION OF TUBERCULOSIS IN THE HUMAN LUNG.

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As revealed by Roentgen ray examinations, primary or initial infections by the *Mycobacterium tuberculosis* present a varied array of intrathoracic lesions for which the general term Tuberculosis of the Childhood Type was adopted by the American Sanatorium Association¹ in 1929. In the past various designations such as hilum tuberculosis, masked juvenile tuberculosis, infantile tuberculosis, pretuberculosis, latent tuberculosis, concealed tuberculosis, paratuberculosis, epituberculosis, splenopneumonia, gelatinous pneumonia, collateral inflammatory edema, glandular calcifications, Ranke's primary complex, Ghon tubercles, and others have been used in connection with descriptions of primary tuberculosis. The simplification of terminology, accomplished by the American Sanatorium Association, probably will tend to focus attention on primary tuberculosis as a clinical entity manifested by a variety of lesions which collectively represent different retrogressive developmental stages of primary tuberculosis as it customarily occurs in the human lung, whereby the initial or early parenchymal and perihilum infiltrations present in the lung, whether large or small, later slowly resolve to be replaced eventually either by calcified hilum glands alone, or by Ghon tubercles associated with calcium deposits in the adjacent lymph nodes. The end stage of the lesion produced by a primary implantation of tubercle bacilli in the lung parenchymal and the subsequent spread of the infection to the regionally related lymph nodes (which commonly occurs, Rfs. 2 to 23 incl.) often is represented by permanent scars known as Ghon tubercles associated with calcified hilum glands, which collectively constitute Ranke's primary complex. In the earliest stage of this pathologic process, relatively benign parenchymal infiltrations of varied sizes form the most striking feature revealed by Roentgen ray examination. Cases representative of this early stage of (massive?) primary pulmonary tuberculosis have been

reported by various authors (see Refs. 24 to 48 incl.). Often in the reported cases which had this type of lesion the disease was relatively benign, and a general tendency was noted for extensive parenchymal lesions to resolve slowly. Many of these children were followed over long periods of time, giving the authors an opportunity to observe complete restoration to normal health occurring frequently in young infants as well as in older children.

Additional data bearing on this subject of primary tuberculosis are presented in the following report based on observations on 1687 children examined at Lymanhurst School for Tuberculous Children in Minneapolis. Each individual included in this group received an intracutaneous injection of 0.1 mg. of old tuberculin, and during periods of observation ranging from 4 to 11 years, the positive tuberculin reactors have had repeated Roentgen ray and physical examinations. The system established at Lymanhurst by Dr. F. E. Harrington, Commissioner of Health, whereby follow-up contacts are made between the patients and the Minneapolis Public Health Nurses, has offered an opportunity to observe the clinical course of primary tuberculosis in the same individual over a period of a few to several years. This follow-up study of a fairly large group of infected children, in which epidemiologic investigations also have been made, has revealed a clinical picture of primary tuberculosis in children, which during the past 11 years has revolutionized many of the opinions formerly entertained by the members of Lymanhurst Medical staff, not only with regard to the ability of an infant or child to survive a severe primary tuberculous infection of the lungs, but also concerning the customary changes which occur in these lesions as the years go by, as well as concerning the relationship of primary tuberculosis to the adult type of the disease.

The data for the 1687 children (sexes combined) included in the survey are recorded in Table 1, in which the 1108 cases who had a negative reaction to 0.1 mg. of tuberculin are separated from the 579 individuals who had a positive reaction to this amount of old tuberculin. Of the 1108 Mantoux-negative cases, repeated Roentgen ray films of the chest were found to be consistently negative in an average of 90.1 per cent (998 cases) of this group. In general, however, during the span of life included in this study (0 to 17 years) the percentage of negative Roentgen ray examinations tended to decline as age increased. In certain instances lesions were found in the Mantoux-negative group (intrathoracic, glandular calcifications and Ghon tubercles [51 cases, Table 1] which were indistinguishable from those characteristic of certain [late] stages of primary tuberculosis [childhood type of tuberculosis]). This group of 51 cases constituted 4.6 per cent of the 1108 children who had a negative reaction to 0.1 mg. of old tuberculin. Each of these children was given a second Mantoux test, using 1 mg. of old tuberculin, to which not a single individual reacted. This observa-

TABLE 1.—TYPES OF INTRATHORACIC LESIONS FOUND BY ROENTGEN EXAMINATION FOR EACH AGE GROUP IN CHILDREN WITH NEGATIVE AND POSITIVE MANTOUX TESTS.

Age, yrs.	No. of cases.	Negative on Roentgen ray exam., per cent.	Lesions characteristic of primary tuberculosis (childhood type).						Adult type of tuberculosis, per cent.	Pleural thickening, per cent.	Bronchiectasis, per cent.	Pneumonia, per cent.	Pneumothorax, per cent.	
			Resolving parenchymal, per cent.	Questionable calcification, per cent.	Slight calcification, per cent.	Moderate calcification, per cent.	Marked calcification, per cent.	Ghon tubercles, per cent.						
Cases Reacting Negative to the Intracutaneous Injection of 0.1 Mg. of Old Tuberculin. Uninfected Group.														
0 to 1	27	96.3 (26)*	1.8 (1)	3.7 (1)	
2 to 3	57	98.2 (56)	1.8 (2)	2.7 (3)	
4 to 5	112	94.6 (106)	...	1.2 (2)	1.2 (2)	2.5 (4)	1.2 (2)	0.9 (1)	...	
6 to 7	161	93.8 (151)	...	1.1 (2)	4.0 (7)	0.6 (1)	...	2.8 (5)	0.6 (1)	
8 to 9	176	90.9 (160)	...	2.0 (4)	3.0 (6)	3.0 (6)	1.0 (2)	
10 to 11	199	90.5 (180)	...	2.3 (4)	2.8 (5)	1.2 (2)	8.5 (14)	1.1 (2)	0.5 (1)	...	
12 to 13	176	83.5 (147)	...	0.7 (1)	2.8 (4)	3.5 (5)	2.1 (3)	1.1 (2)	...	
14 to 15	144	89.6 (129)	...	3.6 (2)	8.9 (5)	0.7 (1)	...	7.1 (4)	...	0.7 (1)	...	
16 to 17	56	76.8 (43)	1.8 (1)	1.8 (1)	...	
Totals and av.	1108	90.1 (998)	...	1.4 (15)	2.8 (31)	0.2 (2)	0.1 (1)	0.2 (2)	...	3.8 (42)	1.0 (11)	0.5 (6)	...	
Cases Reacting Positive to the Intracutaneous Injection of 0.1 Mg. of Old Tuberculin. Infected Group.														
0 to 1	9	77.8 (7)	11.1 (1)	11.1 (1)	7.7 (1)	7.7 (1)	2.6 (1)	
2 to 3	13	53.1 (7)	30.8 (4)	...	15.4 (6)	2.6 (1)	1.8 (1)	5.1 (2)	...	1.8 (1)	
4 to 5	39	59.0 (23)	15.4 (6)	...	20.0 (11)	3.6 (2)	4.4 (4)	9.1 (5)	...	2.2 (2)	
6 to 7	55	45.5 (25)	7.3 (4)	10.9 (6)	11.1 (10)	4.4 (4)	...	12.2 (11)	...	5.5 (5)	
8 to 9	90	43.3 (39)	6.7 (6)	15.6 (14)	11.0 (10)	7.7 (7)	...	18.7 (17)	...	12.0 (11)	
10 to 11	91	47.3 (43)	2.2 (2)	7.7 (7)	11.0 (10)	7.7 (7)	1.1 (1)	14.1 (13)	3.3 (3)	7.8 (9)	1.7 (2)	0.9 (1)	...	
12 to 13	92	40.2 (37)	...	10.9 (10)	13.0 (12)	5.4 (5)	2.6 (3)	11.3 (13)	4.3 (5)	12.0 (9)	1.3 (1)	
14 to 15	115	43.5 (50)	2.6 (3)	5.2 (6)	15.7 (13)	4.3 (5)	5.3 (4)	8.0 (6)	6.7 (5)	
16 to 17	75	31.7 (26)	1.3 (1)	8.0 (6)	16.0 (12)	6.7 (5)	
Totals and av.	579	44.4 (257)	4.7 (27)	8.6 (50)	13.8 (80)	5.2 (30)	2.2 (13)	11.6 (67)	2.2 (13)	6.6 (38)	0.5 (3)	...	0.2 (1)	

* Actual number of cases in parenthesis.

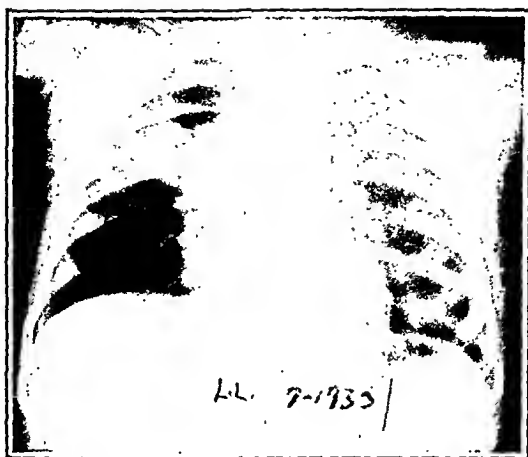


FIG. 1.—Roentgen ray plate, showing parenchymal infiltration (right) due to a primary tuberculous infection of a child, aged 13 months. Plate taken, July, 1930.



FIG. 2.—Roentgen ray taken, April, 1932, of the same child, showing parenchymal infiltration almost completely resolved and replaced by a cluster of calcium deposits. Resolution and complete development of Ghon tubercle required over 21 months in this case during which time this child has not experienced a single day of illness.



FIG. 3.—Roentgen ray taken, in 1921, of boy, aged 10 years, showing 2 conspicuous calcified hilum glands on the right identifying the location of his primary tuberculous lesion.



FIG. 4.—Roentgen ray taken, 1932, of same case as Fig. 3. Shows large calcified gland on the right with no evidence of renewed activity in its vicinity. The other calcified gland is not visualized on this plate. We now find an extensive adult type of tuberculosis throughout the left lung with a small similar type of lesion in the periphery of the right lung. This boy died shortly after this film was taken.

tion strongly suggests that the 51 children in this retested group never had been infected by the tubercle bacillus, in spite of the Roentgen ray evidence to the contrary. The conclusion seems justified, therefore, that in children who have never experienced a primary infection by the *Mycobacterium tuberculosis* as indicated by their negative reaction to relatively large doses of old tuberculin, lesions caused by nontuberculous infections are occasionally found which on the chest films are indistinguishable from those characteristic of primary tuberculosis. This applies particularly to questionable and slight degrees of intrathoracic glandular calcifications (46 cases, Table 1) in which instances the apparent discrepancies may be due in a measure to unavoidable error on the part of an experienced roentgenologist in identifying small calcium deposits. At times the roentgenologist is correct in interpreting the presence of intrathoracic calcium deposits in Mantoux-negative children, since certain nontuberculous infections produce lesions that calcify (Kudlich)⁴⁹ and occasionally these scars may be fairly large, conspicuous and easily identified. Some of the cases of this type may be examples of aspergillus infection. Their incidence in tuberculin-negative children is rather low, however, for among the 1108 Mantoux-negative reactors moderate and marked degrees of glandular calcification and Ghon tubercles associated with calcified glands occurred in a combined total of only 5 cases (Table 1) or 0.45 per cent of this group of children. The data indicate, therefore, that Roentgen ray findings which might be construed as constituting strong evidence of the presence of primary tuberculosis are rarely discovered in children who have a definitely negative Mantoux test.

In a few instances noncalcified lesions due to conditions other than tuberculosis were found in the group of negative tuberculin reactors. These lesions included pleural thickenings (42 children), bronchiectasis (11 children) and pneumonia (6 children), and combined they constituted about 5.3 per cent of this entire group of 1108 children. If the cases found to have questionable and slight intrathoracic glandular calcifications are excluded on the basis of erroneous interpretation of their chest films, under these circumstances lesions due to nontuberculous conditions occurred over eleven times as frequently among the 1108 Mantoux-negative cases, as did conspicuous, easily recognized lesions which are definitely characteristic of primary tuberculosis (moderate and marked calcifications and Ghon tubercles). On the whole, then, the data indicate that in children under 18 years of age who never have been infected by the tubercle bacillus the chest films are negative in the great majority of cases, and then when intrathoracic pathology is revealed by Roentgen ray examination, these findings usually are typical of lesions produced commonly by various nontuberculous infections.

Among the infected children (positive Mantoux reactors) entirely

different conditions were found. Of this group of 579 individuals less than half (44.4 per cent, Table 1) were reported as entirely normal on Roentgen ray examination as compared with an average of 90.1 per cent of similarly negative cases for the group of 1108 children who did not react to tuberculin. The incidence of intrathoracic lesions demonstrable by Roentgen ray films found in the 579 infected children (55.6 per cent) greatly exceeded that (9.9 per cent) discovered in the uninfected cases, and this increase in pathologic findings noted for the former, as compared with the latter group of children, resulted largely from scars produced by the primary tuberculous infections which the positive Mantoux reactors had experienced. The influence of primary tuberculosis in greatly increasing the incidence of lesions demonstrable by chest films becomes evident on further analysis of the data, according to which lesions typical of the primary or childhood type of tuberculosis (resolving parenchymal infiltrations, calcified intrathoracic glands and Ghon tubercles) were found in a total of 46.1 per cent (279 cases; Table 1) of the 579 infected children, as compared with an incidence of 4.6 per cent (51 cases) for similar lesions in the Mantoux-negative group. Attention is also called to the fact that in the infected group the percentage of lesions typical of the childhood type of tuberculosis (46.1 per cent), greatly exceeded the relative incidence (5.3 per cent) of lesions reported for the noninfected group resulting from all nontuberculous pulmonary infections combined. In the positive Mantoux series this is also true when the cases who had questionable and slight calcifications of the hilum glands are excluded. Thus an additional statement seems justified, to the effect that primary pulmonary infections by the *Mycobacterium tuberculosis* occurring during childhood produce conspicuous intrathoracic lesions which are practically unmistakable on the chest film, the incidence of which greatly exceeds that of lesions resulting from all other pulmonary infections combined.

The prevalence of lesion due to various nontuberculous conditions (pleural thickenings, bronchiectasis, pneumonia and pneumothorax) found in the group of tuberculin-positive children, in general, did not differ greatly from that observed for those who had a negative Mantoux reaction. The only essential difference noted between the two groups with respect to these conditions was the greater relative frequency of pleural thickening in the cases who had a positive tuberculin reaction. The increase noted for this type of lesion no doubt was due in part, if not entirely, to the tuberculous infections which this group had experienced as indicated by the observation that primary tuberculous infections frequently produce thickenings of the pleura.

The primary or childhood type of tuberculosis discovered in these children was exemplified by various lesions which may be classed conveniently into three main groups, namely, resolving

parenchymal infiltrations, glandular calcifications and Ghon tubercles. The earliest and most extensive of the lesions characteristic of primary tuberculosis are represented by parenchymal infiltrations, of which 27 examples were discovered. In general these parenchymal lesions were relatively more frequent in the younger than in the older groups of children, and their combined incidence amounted to 4.7 per cent (Table 1) of the entire group of 579 positive Mantoux reactors. In each of these 27 children the parenchymal infiltrations have slowly resolved, although in every case many months were required before complete resolution was accomplished (See Figs. 1 and 2). Accompanying or following the final disappearance of these infiltrations calcium deposits have appeared, located usually within the related lymph nodes as well as in the area previously occupied by the infiltration. Later, in the majority of these children gradually increasing amounts of calcium appeared at sites of these foci, resulting eventually in the production either of calcified glands alone or of well-defined Ghon tubercles, associated with calcifications of the adjacent hilum nodes. The follow-up study of these cases at Lymanhurst has given us an opportunity to follow carefully all the various stages through which these extensive early primary parenchymal lesions pass, leading finally to their complete disappearance and replacement by calcified scars. Up to the present time I have had the privilege of observing 73 infants and children in whom lesions of this type were present. Two of these cases have been under observation for 9 months, a third for 28 months, and the remaining 68 cases have been watched for periods ranging from 3 to 9 years; and during this time no deaths have occurred in any of these 73 children. A few years ago we expected all of the cases having extensive parenchymal infiltrations to die soon of tuberculosis, particularly when the condition was found in young infants. Today we expect every case of this type to survive if protected thereafter from reinfection.

During the 11 years the follow-up study has been in progress at Lymanhurst not a single child has died of a primary tuberculosis. If deaths do result from primary infections by the tubercle bacillus, the experience at Lymanhurst indicates that such occurrences are rather rare during infancy and childhood. In most cases (all in our experience) extensive parenchymal lesions resolve and disappear leaving relatively inconspicuous calcified scars and, during the months this resolution is taking place, the patient, whether a young infant or an older child, may enjoy excellent health. At times severe and alarming symptoms are present for variable periods early in the course of the disease, following which a long period of symptomless convalescence ensues. This experience is very impressive in revealing the remarkably efficient power with which infants and children alike are endowed by Nature to overcome a primary tuberculous infection. As a result of past experience I feel that in the

dosage ordinarily received in human experience a single primary infection by the tubercle bacillus ordinarily fails to kill an infant or child who is in good health at the time the initial infection occurs.

The other lesions representative of the childhood type of tuberculosis included the glandular calcifications and Ghon tubercles, and among the 579 positive Mantoux children the incidence of the former (29.9 per cent, 173 cases) greatly exceeded that of the latter (11.6 per cent, 67 cases, Table 1). Of infected children, therefore, the data indicated that the calcified intrathoracic lymph nodes occur much more commonly than do Ghon tubercles. These calcified scars in general are relatively old lesions typical of primary tuberculous infections which occurred months and years ago, whereas their precursors, the resolving parenchymal infiltrations, are comparatively early and fresh lesions. Regardless of the marked difference existing in their appearance on the Roentgen ray film, these early and later lesions merely represent different stages in the evolution of primary tuberculosis as it commonly occurs in the human lung, and collectively they constitute the complete Roentgen ray picture of the clinical condition spoken of as the childhood type of pulmonary tuberculosis.

In this study 13 children were found who had consumption. The diagnosis of the adult type of tuberculosis was made in these cases after repeated Roentgen ray examinations, which revealed mottled subapical lesions which later tended to spread and to form cavities. At the Lymanhurst School only cases of primary tuberculosis are admitted, so these 13 children were transferred either to hospitals or to sanatoriums for further treatment, and in this group of cases the mortality has been high. The adult type of tuberculosis has developed in certain of these children, postdating several years the known presence of scars due to primary tuberculosis. This is illustrated by the case whose Roentgen ray films taken in 1921 and 1932 are shown in Figs. 3 and 4. Eleven years ago this boy had a positive tuberculin reaction, and on Roentgen ray examination (Fig. 3) marked calcification was found in the hilum glands on the right side, identifying the location of his primary tuberculosis. Eleven years later his Roentgen ray films (Fig. 4) show an extensive mottled tuberculous infiltration of the opposite lung and a small lesion in the periphery of the right lung. At this time, however, the calcified glands discovered long ago show no tendency toward breaking down, thus there is no Roentgen ray evidence that his phthisis resulted from a lighting up of the old infection acquired 11 or more years previously. In this case his consumption is confined almost exclusively to the lung opposite to that in which the primary focus is located, and an illogical stretch of the imagination is required to suggest that this lesion on the left resulted from a lighting up of this old lesion on the right, rather than being caused by an exogenous reinfection. Other cases similar to this have been observed at

Lymanhurst, in which as Roentgen ray films are taken year after year: new lesions have appeared postdating the known presence and location of older primary tuberculous foci, developing as frequently in the opposite as in the same lung in which the calcified primary lesion was located. Neither at the time of the appearance of these new infiltrations, nor later, has any case been discovered in which the Roentgen ray examination revealed evidence of a reactivation of the previously existing old calcified scars of primary tuberculosis. Furthermore, these old calcified scars have remained unchanged throughout the entire course of the subsequently developed consumption. On Roentgen ray examination immediately before death ensues they still appeared to be as quiescent as they were before the adult type of tuberculosis developed. This failure to find evidence of consumption resulting from a breaking down of calcified lesions of primary tuberculosis suggests that phthisis does not result from a reactivation of an infection acquired in childhood, but develops rather following a reinfection (received in sufficient dosage to produce a parenchymal lesion) of an individual whose body already harbors a focus of primary tuberculosis. This implies that an initial infection by the tubercle bacillus alters the immune reaction of the human body in such manner that the soil is prepared for the development of the adult and killing type of tuberculosis in these individuals when reinfections later occur in sufficient dosage to produce parenchymal infiltration in the lungs. To date we have not seen phthisis develop following a primary tuberculous infection in any child who was known to have a negative Mantoux test previous to the time the initial infection took place. Following such an experience these children uniformly develop the benign type of tuberculosis which eventually calcifies. In children in whom the Mantoux test was known to be positive and who had calcified scars of primary tuberculosis, we have not seen the benign childhood type of tuberculosis develop a second time. In our experience the human body can reduce an infection into what is known as a primary complex only once, and if these individuals later develop additional tuberculous lesions these new infiltrations are always of the type characteristic of phthisis. In this connection it is interesting to note that von Behring⁵⁰ held that phthisis resulted from a reinfection of a person infected with the bacillus during childhood. Orth⁵¹ has furnished pathologic evidence that old lesions need not show evidence of recent activity, and that acute tuberculous reinfection may supplant a quiescent one and cause death. Bachmeister⁵² could produce typical apical phthisis in rabbits only when a previous tuberculous infection had occurred somewhere in the animal. He concludes that for the production of typical phthisis a relative immunity of the body is necessary, and this is produced by an early primary infection. On careful postmortem examination Opie⁵³ found that apical tuberculosis in the lung of adults is always

accompanied by evidence of coexisting focal tuberculous infection of the childhood type. In cases of active pulmonary tuberculosis he always finds evidence of preceding tuberculous infection. The possibility of an interrelationship existing between the appearance of sexual maturity and the development of consumption following reinfection of previously infected children is suggested by the tendency for the adult type of tuberculosis to make its appearance during the teens. It was during this period of childhood exclusively that the 13 cases of the adult type of tuberculosis were found in this series of 579 infected children. On the basis of the findings in this group of cases combined with a larger experience of over 9000 children examined at Lymanhurst during the past 11 years, the following outline is offered as representing the conception this experience has given with regard to the evolution of tuberculosis in the human lung.

Summary. 1. Primary tuberculous infections of the lungs are revealed by the Roentgen ray films as parenchymal infiltrations, calcified glands and Ghon tubercles.

2. These lesions although varied in appearance merely represent different stages in the development of one and the same clinical condition, namely primary tuberculosis, or tuberculosis of the childhood type.

3. The general tendency for lesions resulting from an initial infection by the tubercle bacillus is first to resolve and later to calcify.

4. The human body can resolve a tuberculous infection into what is known as the primary complex only once.

5. When once reduced to calcified scars these primary tuberculous lesions do not become reactivated later in the production of the adult type of tuberculosis (consumption).

6. Death seldom and possibly never results from a single primary pulmonary tuberculous infection. The prognosis is excellent in infancy as well as in later childhood, provided reinfection is prevented.

7. Primary tuberculous infections of the lung, if extensive, produce symptoms of varying severity, which subside in the course of a few to several weeks. Thereafter, throughout the remainder of the life of the patient these primary lesions produce no clinical symptoms. (Occasionally a very large Ghon tubercle acting as a foreign body may erode a bloodvessel and cause hemoptysis, and in rare instances may be expelled from the lung in coughing.)

8. Consumption (plithisis) does not develop as a result of an initial infection by the tubercle bacillus. The first infection occurring at any age in life uniformly resolves and calcifies.

9. Consumption develops following a reinfection of individuals who previously have had a primary infection.

10. The reinfections responsible for the development of plithisis are probably exogenous in origin in the majority of cases.

11. The lesions of reinfection (adult type of tuberculosis or phthisis) usually appear in the subapical portions of the lungs.

12. These lesions may be present for months and years, without producing symptoms, physical findings or showing any tendency to spread.

13. During the teens previously dormant lesions characteristic of the adult type of tuberculosis frequently tend to spread, to produce cavities and to cause death.

14. The adult type of tuberculosis seldom calcifies.

15. Puberty seems to favor the breaking down of previously existing apparently quiescent subapical infiltrations of the adult type of tuberculosis. Primary infections occurring during puberty, however, behave much the same as do similar infections taking place in infancy and early childhood.

16. Lesions of the adult type of tuberculosis tend to spread and cavitate, whereas infiltrations resulting from initial tuberculous infections tend to recede and calcify.

17. The prognosis is grave for the adult type of tuberculosis. This type of the disease frequently results in death, whereas primary infections are seldom fatal.

18. The relationship existing between the childhood and the adult type of tuberculosis seems to consist largely in the tendency for the primary infection to prepare the patient for the development of phthisis should he perchance later experience a reinfection of sufficient severity to produce an intrapulmonary lesion.

19. Phthisis apparently does not customarily result from a lighting up of an old infection received in childhood.

20. The part that the former childhood infection seems to play in favoring the later development of phthisis seems to depend more upon the changes which this primary infection caused with respect to the manner in which the body reacts thereafter to the tubercle bacillus and its products, rather than upon a lighting-up of the old disease acquired during childhood.

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INTESTINAL OBSTRUCTION CAUSED BY FOOD.

CASE REPORT.

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IN a recent report Elliott reviewed the literature on intestinal obstruction caused by food and found 39 cases of this type which had been reported since 1910. Of these cases the diagnosis was confirmed by operation or necropsy in 26 instances, while of the others the diagnosis was doubtful in 5 cases. Of the food material which caused obstruction, orange pulp was the cause in only 1 case,

to which Elliott added his own case which was also caused by this fruit. He states that his case is the first of this kind, proved by operation and necropsy, to be reported in this country. At the time of the appearance of this article I had under my care in the Jewish Hospital a typical case of acute intestinal obstruction which was caused by orange pulp and which might be of interest to record.

Case Reports. A white female, aged 57 years, was admitted on June 27, 1932, at 9.20 P.M., complaining of severe abdominal pain, intermittent in character, and repeated attacks of vomiting. She had been in good health until the day before admission when she developed crampy pain in the midabdomen, which gradually became more severe and was unrelieved by sedatives. An enema which had been given was returned without either feces or gas. Her temperature was 100.4° F., pulse 90 and respirations 22. Her previous medical history was significant only in that she had once had pneumonia and also that she had never had any abdominal operation. Physical examination revealed a short, stout type of individual, the abdominal fat preventing a very satisfactory examination for the presence of masses, but no rigidity was noted. The condition was typical of acute intestinal obstruction of undetermined origin, although on account of her age a carcinoma of the bowel was considered most probable.

Immediate operation was done under ether anesthesia through a lower midline incision. On opening the peritoneal cavity a moderate quantity of clear peritoneal fluid escaped and an examination of the entire colon revealed nothing abnormal. The lower ileum contained a mass between 2 and 3 inches long which felt boggy and completely obstructed the bowel at this point. Although the mass could not be moved very far, it was evident that it was in the lumen and not in the wall of the bowel. An enterostomy was done and a mass of yellow vegetable material was pushed from the bowel. A rubber catheter was sutured into the enterostomy and the abdomen was closed without further drainage. Examination of the specimen after the operation showed that it greatly resembled inspissated sweet potato, but a closer inspection revealed that it was composed of two sections of orange which had become impacted side by side. Positive identification was made by finding a few orange seeds inside the mass and on questioning the patient after the operation she stated that she had eaten oranges about 12 hours before the onset of her pain. Because she had no teeth she swallowed the sections of orange without careful mastication.

After operation all of her abdominal symptoms subsided very promptly. The next day she showed signs of pulmonary trouble which later developed into a bilateral pneumonia and in spite of strenuous efforts at treatment, including continuous use of an oxygen tent, she died on July 7, 1932, 10 days after the operation.

The above case presents most of the features which Elliott found in his review, such as: (1) An edentulous patient; (2) short interval (12 hours) between ingestion of the orange and the onset of obstruction; (3) the site of obstruction was in the lower ileum; (4) failure of accurate diagnosis of the cause of the obstruction; (5) fatal termination following operation, although death was due to post-operative pneumonia as the obstruction had been entirely relieved.

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THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE.

A STUDY OF 235 CASES OF NONHEMOLYTIC JAUNDICE DUE TO CARCINOMA, CALCULUS IN THE COMMON BILE DUCT AND LIVER DEGENERATION.

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THE recognition of diseases in which jaundice is the chief sign is in many instances a difficult diagnostic problem. Numerous laboratory tests for liver function and aids in the diagnosis of biliary tract disease have been developed in the past 20 years, but their application to the differential diagnosis of the causes of nonhemolytic jaundice has been disappointing. For this reason, we have reviewed a number of such cases seen in the Presbyterian Hospital in recent years to ascertain whether any clinical data other than that which is generally appreciated could be found to aid in differential diagnosis.

Cases of nonhemolytic jaundice, where the jaundice is one of the outstanding complaints may, in the main, be divided into three groups to which we have largely confined our attention: (1) So-called catarrhal jaundice and atrophy of the liver (*i. e.*, idiopathic acute yellow atrophy, poisoning by arsphenamin and einchophen); (2) carcinoma involving the pancreas, bile ducts or gall bladder and primary carcinoma of the liver; (3) cases with calculus in the common bile duct. Other causes for nonhemolytic jaundice were not included in this study, either because they were uncommon or because, as in Laennec's cirrhosis, the diagnosis usually offers less difficulty.

All the cases of jaundice due to either neoplasm or calculus in the common bile duct were proven either by operation or by autopsy. The cases of catarrhal jaundice were not proven by these two methods, but all ran the usual course of that disease and were followed to the complete disappearance of their symptoms and often

much longer. Most of the cases of acute yellow atrophy came to autopsy and the rest presented the typical symptom complex of that condition.

The following table gives the number of cases included in this series:

CASES OF JAUNDICE STUDIED.

Group I:	Cases.
Catarrhal jaundice	81
Arsenic poisoning	15
Acute yellow atrophy	17
Group II:	
Carcinoma of pancreas	30
Carcinoma of bile duct	9
Carcinoma of gall bladder	10
Primary carcinoma of liver	7
Group III:	
Calculus in common bile duct	66
Total	<hr/> 235

Results of Analysis of Cases. *Age.* Age is of considerable importance in differential diagnosis. Pronounced icterus in younger individuals is usually due to what is known as catarrhal jaundice. Of the patients with catarrhal jaundice and acute yellow atrophy 80 per cent were below the age of 40 years. The youngest patient with acute yellow atrophy was 29 years of age, and in general it may be said that the older the patient with signs suggesting catarrhal jaundice, the more likelihood there is of the condition progressing to atrophy of the liver.

In contrast with the catarrhal jaundice group, over 80 per cent of the patients with either calculus in the common duct or carcinoma with jaundice were over the age of 40 years. The cases of arsphenamin jaundice occurred in the same age groups as did those of carcinoma and stone in the common duct, being evenly distributed through the decades after the age of 30 years.

Sex. Sex distribution merely confirmed the figures frequently reported. There was a slight predominance of males in the catarrhal jaundice group and of females in the acute yellow atrophy group. In the carcinoma group, however, sex is of more significance. In the carcinoma of the gall bladder group 71 per cent of the patients were females and most of those with primary carcinoma of the liver were males. Carcinoma of the bile duct was slightly more common in males than in females. Of the patients with calculus in the common bile duct 71 per cent were females.

Degree of Jaundice on Admission. Patients with carcinoma of the pancreas, gall bladder or bile duct usually presented a moderate or intense degree of jaundice when first seen. In primary carcinoma of the liver the jaundice was slight, if present at all. In patients with calculus in the common bile duct the degree of jaundice on admission to the hospital was extremely variable—approximately equal numbers presenting a jaundice which was described as slight, moderate or intense. This was also true of the cases of catarrhal jaundice and necrosis of the liver.

Duration of Jaundice on Admission. In the patients with catarrhal jaundice and acute yellow atrophy the jaundice had existed in the majority of instances less than 2 weeks. In the carcinoma group, on the other hand, the patients had usually noticed the presence of jaundice at least a month before entry and in some cases much longer.

In the patients with calculus in the common bile duct the duration was quite variable. Many patients described it as intermittent or varying in

intensity. These features were very seldom mentioned by any of the patients who had carcinoma or catarrhal jaundice. Many of the patients with stone in the common duct gave a history of a previous attack of jaundice and a fair proportion of them were first seen at a time when the jaundice was subsiding. The presence of any of these features in the history of a patient with jaundice weighs heavily against carcinoma and in favor of stone in the common duct.

Initial Symptoms. The initial symptom in catarrhal jaundice and liver necrosis was extremely variable but interesting in comparison with the other two groups. It was most commonly nausea or vomiting but frequently malaise, jaundice, epigastric pain or anorexia. One case had a chill at onset.

In the group with carcinoma approximately one-half of the patients gave pain in the upper abdomen as the first symptom. The next most common initial symptom was jaundice and in a small percentage of cases the first indication of illness was weakness or pruritus. Abdominal pain was the chief initial symptom in individuals with stone in the common duct. A few patients mentioned fever, rigor or jaundice as their first complaints.

Abdominal Pain. The incidence of pain in the three groups of patients is of considerable interest from the standpoint of diagnosis. Some type of abdominal pain or discomfort was present in the majority of cases in all the groups.

Slightly more than one-half of the patients with catarrhal jaundice and necrosis of the liver complained of some type of upper abdominal distress. This varied from sharp pain to vague discomfort—a greater number complaining of the latter.

Pain was present in the majority of cases in all of the types of carcinoma. That it is the most frequent initial symptom of that condition has already been mentioned. Of the entire group of patients with carcinoma 65 per cent had pain. In carcinoma of the pancreas or bile ducts it was apt to be a persistent and boring epigastric pain. In carcinoma of the gall bladder it was frequently sharp and cramp-like. The pain in primary carcinoma of the liver is occasionally sharp but more frequently dull.

In the patients with calculus in the common bile duct, pain was the most important diagnostic sign. It was characteristically severe and cramp-like, located in the epigastrium or in the right upper quadrant and in the majority of cases radiated to the back or shoulder. Two of the 66 patients with stone in the common duct gave no history of pain, causing diagnostic uncertainty until exploration.

Pruritus. In catarrhal jaundice and atrophy of the liver itching is mild when present. In our group it was present in only one-fifth of the cases. On the other hand, nearly all of the patients with carcinoma of the pancreas, gall-bladder or bile duct complained of moderate or severe itching. Itching was usually absent in primary carcinoma of the liver. It was also absent in two-thirds of the patients with calculus in the common duct and variable in degree when present.

Weight Loss on Admission. A history of loss of weight on entry into the hospital was unusual in the catarrhal jaundice and liver necrosis group and common in the other two groups, median for weight lost in each of these being at 20 pounds. The essential difference between these two groups, however, was the fact that in the carcinoma group there was a recent progressive weight loss, whereas in the group with calculus in the common duct the loss of weight was usually intermittent, protracted and associated with frequent digestive disturbances.

Other Symptoms. Weakness as a prominent symptom is worthy of note, for it was an outstanding complaint in practically all of the patients with

carcinoma. It was uncommon in the catarrhal jaundice or stone in the common duct groups, but frequently present in patients who later showed signs of acute yellow atrophy. In 21 cases of catarrhal jaundice (25 per cent) there was a history of upper respiratory infection at the onset, whereas such a history was rare in the other groups.

Fever. The majority of the patients with catarrhal jaundice and liver necrosis ran a temperature which exceeded 100° F. and in a few instances reached 102° and 104°. On the other hand, in carcinoma of the pancreas with jaundice, fever was rarely present, there being only 1 individual in the group with a temperature of more than 100° F. by rectum before operation. In the other types of carcinoma producing jaundice, fever was a common occurrence. Likewise, in the cases with calculus in the common bile duct fever was usually present.

Tenderness in the Upper Abdomen. Tenderness over the liver was present in over one-half of the cases of catarrhal jaundice and necrosis of the liver, and in one-third of the patients with stone in the common duct. It was absent in the group with carcinoma.

Liver Size. In jaundice due to carcinoma the liver was found to be enlarged in most cases on admission to the hospital. This applies to all of the types of carcinoma considered here.

It is difficult to speak categorically of the size of the liver in catarrhal jaundice and liver necrosis from the data at hand, as the patients were not all seen at the same stage of the disease. In reviewing the individual cases, however, the impression is confirmed that the liver usually increases in size early in the disease and may be felt 2 to 4 cm. below the costal margin in the right midclavicular line. Later, it recedes to or beneath the costal margin. This shrinkage of the liver in the later stages of the disease, associated at times with a marked diminution of the liver dullness, is the event which gives cause for alarm, except when this change is noted during convalescence. When there is persistent vomiting increasing jaundice and bile remains absent from the stools in patients who are thought to have catarrhal jaundice, progressive atrophy of the liver may be suspected. In the group of patients with calculus in the common bile duct the liver was usually found to be enlarged.

Enlargement of the Spleen. The presence of a palpable spleen is a definite aid to diagnosis. It was considered to be enlarged on admission in 19 (26 per cent) of 66 cases of catarrhal jaundice. It was palpable in a corresponding proportion of the cases with arsenic necrosis of the liver and acute yellow atrophy.

In carcinoma of the pancreas the spleen was found to be enlarged in only 2 cases. One of these patients also had myeloid leukemia and the other had marked biliary cirrhosis. The latter case is of interest in that the splenomegaly and also a positive Wassermann test led to the erroneous pre-operative diagnosis of syphilis of the liver.

The spleen was enlarged in only 1 patient in the group with calculus in the common duct. This patient had developed a terminal septicemia and was found to have a large acute splenic tumor at autopsy.

Gall Bladder Size. Palpation of the gall bladder when compared with the operative findings was shown to be rather inaccurate. In the majority of the cases of carcinoma of the pancreas, bile duct and gall bladder, enlargement of the gall bladder was demonstrated at operation, although in over one-half of these cases it had not been recognized on examination of the patient.

It was of interest to find that one-fourth of the patients with calculus in the common bile duct had enlargement of the gall bladder at operation. This was usually associated with a chronic cholecystitis. In most of these cases the gall bladder had been accurately palpated before exploration.

In the catarrhal jaundice group there were 2 patients in whom the gall bladder was thought to be enlarged on physical examination. This led to the diagnosis of carcinoma of the pancreas, which was later shown to be erroneous when the patients' symptoms disappeared completely.

Ascites. Ascites was uncommon in the cases studied. It occurred late in a number of cases of acute yellow atrophy. It was present in 6 of the 7 cases of primary carcinoma of the liver and in 1 case of carcinoma of the pancreas. Ascites in these instances was usually associated with a concomitant hepatic cirrhosis. It was absent in the group with calculus in the common duct, except in 1 patient who also had Laennec's cirrhosis.

Diabetes. An additional aid in the diagnosis of carcinoma of the pancreas with jaundice is the presence of diabetes mellitus. Seven of the 30 cases in this series had a persistent glycosuria. Furthermore, the onset of the symptoms of diabetes in a few cases seemed to coincide with the development of the carcinoma.

"Amin Breath." The peculiar pungent odor of the breath frequently detected in acute yellow atrophy was rarely mentioned in the records. It is not usually observed early in the disease and is of little help in early diagnosis. Its presence was mentioned in 9 of 16 cases in this series and also in 1 case of arsenic poisoning with jaundice. Subsequent experience has suggested that, if it had been sought for, it might have been noted frequently in the more severe cases of catarrhal jaundice. There was no mention of "amin breath" in the records of patients with stone in the common duct or carcinoma.

Additional Signs. A number of other significant signs in these cases deserve comment. Some form of hemorrhage was observed 3 times in severe catarrhal jaundice and 10 times in acute yellow atrophy. The presence of a rash may aid in confirming the diagnosis of acute yellow atrophy or catarrhal jaundice. The rash when present is usually acneform, although in 2 cases it was erythematous.

The presence of edema, of neurologic signs, or low blood urea or uric acid and high blood amino acids occurring late in the course of acute yellow atrophy is of no aid in early diagnosis.

Stool Bile on Admission. One of the mainstays in the differential diagnosis of jaundice is the mercuric chlorid test for urobilin in the stool. In our series this test was found to be of most significance in the diagnosis of carcinoma of the pancreas, for in almost every case it was negative. This test was also negative in all but 1 of the cases of carcinoma of the gall bladder or bile duct. It was always positive in primary carcinoma of the liver.

The results were by no means so uniform in the group with calculus in the common duct. In only 40 per cent of those cases in which the test was reported was it negative. The mercuric chlorid test was negative in approximately the same percentage of those patients who had catarrhal jaundice and liver necrosis. It can, therefore, be of no help in differentiating the latter group from the cases with calculus.

Erythrocyte Count. The red blood count is generally of little aid in the differential diagnosis of the types of jaundice considered here. Anemia was slight when present in the patients with carcinoma.

Leukocyte Count. Leukocytosis of some degree was found in a considerable number of cases in all of the three groups. In the catarrhal jaundice and liver necrosis group the white count exceeded 10,000 per c.mm. in one-fourth of the cases. A slightly larger proportion of the cases of carcinoma with jaundice presented some degree of leukocytosis.

Serum Bilirubin. The serum bilirubin was not determined in the majority of instances. From the figures obtained, however, it appears that the highest values tend to occur in catarrhal jaundice and acute yellow atrophy. Serum bilirubin values which exceed 25 mg. per cent usually

indicate liver degeneration. Experience with the van den Bergh reaction leads us to believe that it is useful in differentiating hemolytic from non-hemolytic jaundice, but that it is of no aid in differentiating between the types of jaundice which are considered in this study.

Analysis of Errors in Diagnosis. Errors in diagnosis were most frequent in the group of patients with carcinoma. In many instances various clinical opinions included all of the chief causes of nonhemolytic jaundice. Some of the patients with carcinoma were regarded as having cholelithiasis. This error appears to have been dependent upon the history of epigastric pain in these cases. It has already been emphasized that epigastric pain is an early and prominent symptom in carcinoma. Another error frequently made in the diagnosis of carcinoma was attributable to the coincidental presence of a positive blood Wassermann test. The latter finding often led to a diagnosis of syphilis of the liver, in spite of the fact that a positive Wassermann test in the presence of jaundice is always open to doubt. Syphilis of the liver as a cause of jaundice in the adult has been a very uncommon finding in the cases studied in this hospital for the past 10 years.

There were very few errors in the diagnosis of cases with jaundice due to stone in the common duct. In this group the suggestive character of the pain, the sudden onset of the symptoms, the frequent presence of right upper quadrant tenderness and leukocytosis usually suggested the nature of the underlying process.

Errors in diagnosis were relatively frequent in the catarrhal jaundice group. The patient was often suspected of having carcinoma. The main reasons for such an error appear to have been: (1) Advanced age of the patient; (2) a history of weight loss; (3) the apparent presence of an enlarged gall bladder. These features in themselves might be expected to lead to diagnostic errors, but in these cases other findings should have argued strongly against neoplasm. Several cases of acute yellow atrophy were incorrectly diagnosed for similar reasons.

If there are several factors concerned in the production of the disease picture, such as coincident calculus in the gall bladder and carcinoma, the opportunities for error in diagnosis are greatly increased.

In summary, the outstanding causes for error in the diagnosis of the cases of jaundice in this series were: (1) The high incidence of pain in carcinoma with jaundice; (2) positive Wassermann test; (3) erroneous palpation of the gall bladder.

Differential Diagnosis. It is not practicable to differentiate clinically early in the disease between cases with catarrhal jaundice and cases which are to develop acute yellow atrophy. In fact, the early clinical pictures in these conditions seem to be identical. The symptoms and signs in necrosis of the liver due to some drug, such as arsphenamin or cinchophen, are the same as those seen in catarrhal jaundice or acute yellow atrophy, with the exception that patients with the latter conditions may give a history of antecedent upper respiratory infection. Where the history of the exhibition of such a drug can be obtained, however, the diagnosis of liver necrosis or "toxic hepatitis" is facilitated.

The diagnosis of catarrhal jaundice in the middle-aged individuals may be difficult. Of particular assistance in making this diagnosis may be: (1) The usual short duration of the jaundice at the time when the patient feels sick enough to present himself for examination; (2) the usual vagueness of the presenting symptoms, namely,

a moderate degree of dull epigastric pain, malaise, anorexia and nausea or vomiting. Weakness is not an outstanding complaint in these cases, as it is in carcinoma, and there is seldom a history of antecedent loss of weight. Itching is usually absent, and if present it is slight. When the spleen can be felt it is an important aid in diagnosis. Tenderness over the liver is present in over one-half of the cases. Minor signs which may be of assistance are the "amin breath" and an acneform eruption. A very high serum bilirubin favors the diagnosis of catarrhal jaundice or acute yellow atrophy rather than carcinoma or calculus.

Calculus in the common bile duct offers few difficulties in diagnosis when there is a history of one or more attacks of the characteristic pain with local tenderness and leukocytosis. When the pain is absent, however, the diagnosis is difficult and such cases are apt to be regarded as carcinomatous. The very considerable loss of weight which may attend this condition may also be misleading.

TABLE 1.—SIGNS AND SYMPTOMS IN 235 CASES OF NONHEMOLYTIC JAUNDICE.

	I. Catarrhal jaundice, acute yellow atrophy, arsphenamin jaundice.	II. Carcinoma of pancreas, gall bladder, bile duct, liver (primary).	III. Calculus in common bile duct.
Age	80% under 40 years	80% over 40 years	80% over 40 years.
Sex	Catarrhal jaundice, 67% males; acute yellow atrophy, 76% females; arsphenamin jaundice, 53% females	Pancreas, 72% males; gall bladder, usually females; bile duct, even- ly divided; liver, usu- ally males	71% females.
Degree of jaundice on admission	Variable	Marked, except in pri- mary carcinoma of liver	Variable.
Duration of jaundice on admission	Less than 2 weeks in 78%	More than 3 weeks in 65%	Often intermittent, re- current or subsiding.
Chief initial symptom	Anorexia, nausea, vom- iting or malaise, 60%	Pain, 48%; jaundice, 27%	Pain, 85%.
Upper abdominal pain or discomfort	Present in 56%	Present in 65%	Present in 97%.
Pruritus	Usually absent and mild when present	Almost always present except in primary car- cinoma of liver	Variable.
Loss of weight . . .	Usually none	Average, 20 pounds	Average, 20 pounds.
Asthenia	Usually absent	Usually present	Usually absent.
Prodromal upper res- piratory infection	Present in 25%	None	None.
Fever	Usually present	Pancreas, usually absent; gall bladder, present; liver, present; bile duct, present	Present.
Upper abdominal ten- derness	Present in 55%	Absent except in primary carcinoma of liver	Present in 29%.
Liver size	Enlarged early	Enlarged	Enlarged.
Spleen	Palpable in 25%	Not palpable	Not palpable.
Diabetes mellitus . .	Absent	Pancreas, present in 23%	
Acneform eruption . .	Often present	Absent	Absent.
Stool bile	Variable	Pancreas, gall bladder, bile duct, persistently negative; liver, positive	Variable.

The important features disclosed concerning carcinoma of the pancreas with jaundice are: First, that pain is the commonest initial symptom and is present early in the disease in the majority of cases. This pain is usually dull, boring and epigastric in location. Bile is usually absent from the stool and itching is almost always

present, which is true of neither catarrhal jaundice nor calculus in the common duct. When the patient is first seen the jaundice is usually intense. He gives a history of a considerable loss of weight and weakness is an outstanding complaint.

On physical examination the liver is enlarged but not tender and the spleen cannot be felt. Palpation of the gall bladder is at best a very deceptive physical sign, but in many instances it is found enlarged at operation. It must be remembered, however, that one-fourth of our cases of calculus in the common duct were also found to have enlarged gall bladders at operation. Fever is usually absent. The presence of diabetes mellitus, apparently of recent onset, may be of additional help in diagnosis.

In carcinoma of the bile duct or gall bladder the clinical picture is usually not very different from that seen in carcinoma of the pancreas and, in general, it is dangerous to hazard an opinion as to the exact location of a neoplasm obstructing the biliary tract. If, however, the patient is a female and gives a history of previous attacks suggestive of cholelithiasis and is running a fever, the palpation of a mass in the region of the gall bladder may suggest the diagnosis of carcinoma of the gall bladder.

Primary carcinoma of the liver should be suspected in a patient who shows evidence of cirrhosis of the liver, who gives a history suggestive of some type of neoplasm and who has fever, upper abdominal pain and jaundice of slight degree.

Conclusion. The records of 235 cases of nonhemolytic jaundice have been reviewed in order to determine what clinical evidence may be of assistance in differential diagnosis. The chief findings are summarized in Table 1.

THE INTERRELATION OF PERNICIOUS ANEMIA AND IDIOPATHIC HYPOCHROMIC ANEMIA.*

THE STUDY OF A FAMILY IN WHICH BOTH CONDITIONS OCCURRED SINGLY AND COMBINED.

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THE medical literature reveals considerable evidence to prove an interrelationship between pernicious anemia and idiopathic hypochromic anemia. Disturbances of the gastrointestinal tract, typi-

* Presented at the Meeting of the American Society for Clinical Investigation held at Atlantic City on May 2, 1932.

fied by absence of free hydrochloric acid in the gastric juice, are closely linked with both diseases. The importance of this fact in relation to pernicious anemia has been shown by the now generally accepted work of Castle and his coworkers.¹ Recent reports on idiopathic hypochromic anemia with achlorhydria, by some called by other names—cryptogenetic achylic chloranemia,² simple achlorhydric anemia,³ idiopathic hypochromemia⁴—have emphasized the association of achlorhydria with a hypochromic blood picture. The work of Mettier and Minot⁵ has suggested that achlorhydria may alter the absorption or utilization of iron of the food in this disease.

Hypochromic anemia, as well as pernicious anemia, is found quite commonly in individuals with achlorhydria,^{6,7,8,9} including those who have undergone operations upon the stomach.^{10,11} Of especial significance are reports of hypochromic anemia developing in members of families in which pernicious anemia occurs.^{3,12,13,14,15,16,17,18,19,20} Minot²¹ has seen at least 10 such instances. Strauss²² has observed 2 patients with marked hypochromic anemia associated with pregnancy whose mothers suffered from pernicious anemia. Achlorhydria in members of the families of pernicious anemia patients is well known. Wilkinson and Brockbank¹⁹ collected from the literature 17 families in which 2 or more members had achlorhydria without pernicious anemia, 59 families in which pernicious anemia and achlorhydria existed in different members and 139 families in which 2 or more members were affected with pernicious anemia. Others^{3,18,19,23,24,25,26,27,28,29} have reported and Minot²¹ has observed pernicious anemia developing in patients who had previously been shown to have an idiopathic hypochromic anemia. Prior to 1872, Biermer³⁰ apparently had observed "chlorosis" preceding pernicious anemia. Patek remarked that "anemia of the secondary type has frequently been known to be a precursor of the primary form." Gram even postulated a stage in the development of pernicious anemia in which there may be a temporary simple anemia curable by iron.

It is a common experience in the treatment of pernicious anemia by liver therapy to observe a fall in color index as the red blood cell count rises—frequently to 0.7 and even less. If iron therapy is then introduced the hemoglobin may rise and the color index approach unity.³¹ In this clinic there have been seen several striking examples of this "splitting" of response to therapy when material potent for pernicious anemia has first been administered and then iron following the subsidence of regenerative signs due to the effects of the potent material.³² In pernicious anemia the tendency of the reticulocyte response to potent material to be smaller the lower the color index, as described by Minot and Heath,³³ may be explained if the prevalence of hypochromic, iron-responding anemia in patients with achlorhydria is born in mind.

It is reasonable, therefore, that the two conditions may coexist.

Cases of anemia have been reported with a low color index, but a normal or increased cell size. These individuals, as Watkins,³⁴ Davics⁹ and we³⁵ have observed, may respond in a degree to liver as well as to iron. However, this situation may occur in anemic states which undoubtedly are not related to Addisonian pernicious anemia; for example, anemia due to subacute blood loss and arising in pregnancy. A hypochromic blood picture in subacute combined degeneration of the cord has been observed.^{3,23,36} Such a condition undoubtedly occurs occasionally, but these cases are probably instances of coëxistence of pernicious anemia and idiopathic hypochromic anemia. A megalocytic anemia is, of course, very much more apt to be present in untreated cases of this type.

A striking example of the interrelation of idiopathic hypochromic anemia and pernicious anemia is here presented. Observations are recorded on 10 individuals with the record of their unusual family history. The study brings up interesting additional problems, and suggests an attractive hypothesis concerning the etiology of such a combination. The opportunity to study this family is due to Dr. George R. Minot, who remembered investigating at the Massachusetts General Hospital in 1916 and 1917 2 sisters, each suffering from a puzzling type of anemia. They were not observed again until 1931, when they came to this clinic in response to inquiry. The family lived about 80 miles from Boston, which rendered the examinations necessarily infrequent and made it difficult to observe all members.

Methods. The blood cell counts were made with U. S. Bureau of Standards pipettes and counting chamber. The hemoglobin was determined by a Sahli hemometer which had been standardized by determinations of the oxygen capacity of the blood by the van Slyke method. One hundred per cent hemoglobin is taken as 15.6 gm. per 100 cc. or 21 volumes per cent oxygen capacity. The mean corpuscular volume³⁷ varied in normal individuals from 85 to 95 cu. micra. The tests of the fragility of the red blood corpuscles were made by adding to 1 cc. of varying concentrations of sodium chlorid solution 0.1 cc. of a 20 per cent suspension of washed corpuscles. The average extremes of beginning hemolysis and complete hemolysis in normal blood were respectively 0.48 and 0.27 per cent sodium chlorid. In performing the gastric analyses, 50 to 100 cc. of 7 per cent alcohol was first given, and if no free hydrochloric acid was present in 40 minutes histamin was injected subcutaneously and the contents examined every 20 minutes for 1 hour afterward.

Family History. Each member of the first generation of this family was born in Scotland. Little is known about their ancestors, but there was no knowledge that any had suffered from anemia or "nerve disease." The family relationship and summary of findings is shown in Table 1.

First Generation. The mother died at 73 years of age of "sugar diabetes." She had a stroke in 1923, living only 6 months thereafter. As a younger woman she was known to complain of a sore mouth, but she was always strong and well. It was never known that she had any trouble with her blood. She raised 10 children and had no difficulties with the pregnancies. However, all her life she had "terrible headaches" nearly

HEATH:

every week, generally unilateral. Her mother died at 57 years of age, cause unknown, and her father died at 79 years of age, of "old age."

TABLE 1.—SUMMARY OF THE IMPORTANT FINDINGS IN MEMBERS OF THE FAMILY.

Generation	I.	II.										III.				
		♀	♂	♀	♂	♀	♂	♀	♂	♀	♀	♀	♂	♂	♀	♀
Sex		♀	♂	♀	♂	♀	♂	♀	♂	♀	♀	♀	♂	♂	♀	♀
Age				59	55	53	52	50		42	41	35	28	26	23	21
Anemia				(+)	+	+	+	Sl.		+	+	+	+	+	+	+
Megalocytosis				+	+	+	+	+		+	+	+	+	+	+	+
Microcytosis				+	+	+	+	+		+	+	+	+	+	+	+
Fragility, r.b.c.				+	+	+	+	+		+	+	+	+	+	+	+
Gastric juice HCl				+	+	+	+	+		+	+	+	+	+	+	+
Diarrhea				+	+	+	+	+		+	+	+	+	+	+	+
Menorrhagia				+	+	+	+	+		+	+	+	+	+	+	+
Migraine				+	+	+	+	+		+	+	+	+	+	+	+
Easy bruising				+	+	+	+	+		+	+	+	+	+	+	+
Thyroid gland				+	+	+	+	+		+	+	+	+	+	+	+
History of cholecystitis				+	+	+	+	+		+	+	+	+	+	+	+
Restricted diet				+	+	+	+	+		+	+	+	+	+	+	+
Atrophy tongue				+	+	+	+	+		+	+	+	+	+	+	+
Combined system disease				+	+	+	+	+		+	+	+	+	+	+	+
Dystrophy, nails				+	+	+	+	+		+	+	+	+	+	+	+
Splenomegaly				+	+	+	+	+		+	+	+	+	+	+	+
Age at death				33	29	59				35	40					
Remarks		"Diabetic stroke"	"Pneumonia"	"Shock"					"Perfect health"	Anemia	Tb. "hemorrhages"	"Good health"	Obesity	"Tired, bilious attacks"		

The father, aged 81 years, was living and well. He had always been robust and never anemic. His mother died at about 73 years of age, in Scotland, cause unknown. His father died between 40 and 50 years of age, in Scotland, cause unknown.

Second Generation. There were 10 brothers and sisters of the second generation, 5 of whom have been examined. *Andrew M.*, the first member of the second generation, died at 29 years of age of an acute "pneumonia." Before that he was troubled with "asthma." He was never pale.

Elizabeth M., the second member of the second generation, aged 59 years, was first seen at the Massachusetts General Hospital, in 1916, at the age of 45 years. She gave a history of menorrhagia commencing 1 year previously and coincidentally progressive symptoms of anemia. Physical examination revealed a moderately enlarged heart, palpable spleen and normal reflexes. Eye examination showed "vascular disease with an occasional hemorrhage." Blood examination: Red blood cells, 3,000,000 per c.mm.; hemoglobin, 43 per cent (Sahli); "marked anisocytosis and poikilocytosis, some red cells, very fat, others mere shadows," achromia was pronounced; white blood cells, 5400 per c.mm.; neutrophils, 61 per cent; small lymphocytes, 32; large lymphocytes, 7. Blood platelets markedly increased. Fragility test showed hemolysis commencing at 0.45 per cent and complete at 0.18 per cent sodium chlorid solution. Pathologic report of uterine curettings: "Hyperplastic endometritis. Endocervicitis."

Following this she improved, but she was seen 1 year later with a recurrence of symptoms of anemia. There were no tongue symptoms or paresthesias. The scleræ showed jaundice. The spleen was palpable and reflexes normal. A tendency to ecchymoses was noted, as, for example, when venipuncture was done, and petechiæ of the eyelids developed when a stomach tube was passed. Blood examination: Red blood cells, 3,080,000 per c.mm.; hemoglobin, 50 per cent (Tallqvist); white blood cells, 5400 per c.mm.; neutrophils, 48 per cent; small lymphocytes, 36; monocytes and large lymphocytes, 16; blood platelets normal. Normal bleeding and clotting time. Fragility test: Hemolysis began at 0.48 per cent and was not yet complete at 0.22 per cent sodium chlorid solution. Gastric analysis showed absent free hydrochloric acid. A transfusion of blood was given.

In 1922 her physician reported that the red blood cells were 3,000,000 per c.mm.; hemoglobin, 85 per cent; color index, 1.4. Dr. Minot examined the blood smear at this time and described it as typical of pernicious anemia.

I first saw this individual on February 27, 1931, when she gave the following additional history: Since girlhood she had suffered from menorrhagia, and about 40 years ago was in a hospital because of excessive flow. For 28 years, or since the birth of her sixth child, she had occasions, usually in January of each year, when she suffered from weakness, palpitation, dyspnea and often sore tongue and mouth. For about 15 years she had progressive difficulty in walking and suffered from paresthesias of the fingers and feet. Two years previously she was ill with right upper abdominal pain, jaundice and light-colored bowel movements. At this time she had a severe nosebleed. Menopause occurred 7 years previously, and she had no more flowing. For a year she had diarrhea 2 or 3 times a week. She had frequent headaches of a migraine type. Her diet for many years was very sparse in meat, but contained fruit and vegetables in moderate amounts. She drank 1 quart of milk and 4 cups of tea a day. The patient had been taking daily, for the past year, a potent liver extract derived from only 200 gm. of liver. Previous to this she had for years taken an "iron" medicine.

Marital history: She had been married 40 years; her husband was living and well; she had 6 children, ages 29 to 36 years, 5 girls and 1 boy. None of the female offspring had had menorrhagia or definite anemia except the second eldest (see Hazel M).

Physical examination, which was incomplete, showed a rather obese woman, plethoric, not icteric, with brown-gray hair and blue eyes. Tongue smooth, not atrophic, except at the edges. Moderate diffuse enlargement of the thyroid gland. Biceps, knee and ankle jerks were not obtained. Vibratory sense was absent over tibiæ and malleoli. Abdomen was not examined.

Blood examination: Red blood cells, 4,320,000 per c.mm.; hemoglobin, 89 per cent; color index, 1.03. Red cells showed definite, not marked, abnormal variation in size and shape. No achromia. Mean corpuscular volume, 91 cu. micra (within normal limits). Icteric index, 2. Fragility test: Hemolysis commenced at 0.5 per cent, complete at 0.3 per cent sodium chlorid solution. White blood cells, 7000 per c.mm.; neutrophils, 67 per cent; lymphocytes, 19; monocytes, 6; eosinophils, 8. The neutrophils tended to be multinuclear. Blood platelets normal.

Unfortunately, this patient was not seen again because she died suddenly, 1.5 months later, of "cerebral hemorrhage."

Summary. This patient exhibited the following interesting features: Prolonged menorrhagia with, at times, spontaneous hemorrhages into the skin and from the nose; a hypochromic blood picture with achlorhydria 14 years ago; a megalocytic blood picture 9 years ago; splenomegaly; at

present evidence of combined system disease, diarrhea and some variation in size and shape of the red cells without anemia, following the ingestion for a year of a potent liver extract; occasionally increased resistance of erythrocytes; history suggestive of cholelithiasis; migraine; enlarged thyroid gland; a diet poor in meat, high in milk and tea. It is believed that she had pernicious anemia in a blood remission, combined system disease, and formerly hypochromic anemia associated with achlorhydria and a poor diet.

Allan M., the third member of the second generation, aged 55 years, was a wire weaver. His first wife died of childbirth. By this marriage he had a daughter who was married and had 2 children, 10 and 4 years of age. All 3 were said to be well. He had been married 15 years to his second wife, who was well except for "bronchitis." She had no pregnancies.

About 3 years previously he began to have attacks of diarrhea, occurring every 3 or 4 months, lasting several days. For about the same period of time he thought he had become somewhat pale and noticed some dyspnea and palpitation on exertion, and weakness. For about 10 years, 2 or 3 times a month, he had headaches, mostly right-sided, coming usually at the end of the week. He had no sore tongue, no numbness, paresthesias or difficulty in walking.

Five years ago he had his upper teeth extracted. His diet contained red meat about 4 days a week, but fruit seldom, and green vegetables only to the extent of a small helping a day. He had suffered from generalized discomfort in the abdomen 25 years ago and was told by his doctor that he had "hyperacidity." No gastric analysis was made. Otherwise he had always been well.

Physiæal examination: Somewhat pale, gray-black hair, light brown eyes, not jaundiced. Tongue coated, not atrophic. Lungs and heart not remarkable. Radial bloodvessels soft but tortuous. Blood pressure: systolic, 105; diastolic, 75. Reflexes normal. Vibratory sense over tibiae present to a normal degree. Blood examination: Red blood cells, 4,715,000 per c.mm.; hemoglobin, 87 per cent. No increased variation in size and shape of the red cells. Mean corpuscular volume, 93 cu. micra. Fragility test: Hemolysis began at 0.48, complete at 0.28 per cent sodium chlorid solution. White blood cells, 6650 per c.mm.; neutrophils, 68 per cent; lymphocytes, 19; monocytes, 7.5; eosinophils, 4; basophils, 1.5. Blood platelets slightly increased. Gastric analysis showed only a trace of free hydrochloric acid 25 minutes after histamin, and no acid 50 minutes after histamin. Peptic activity of the gastric juice was normal.

A few weeks after he had been seen he developed severe diarrhea, with some bloody movements, and he required bed care for several weeks. He was seen again 4 months later when he had recovered from his diarrhea and had gained weight, but felt weak. Blood examination showed: Red blood cells, 4,400,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume, 101 cu. micra. The red cells seemed large but showed very little increased variation in size and shape. He had been on the same diet, and had taken no liver.

The noteworthy features of this case were the hypoacidity, history of diarrhea and migraine, and diet somewhat low in fruit and vegetables but containing appropriate amounts of protein and red meat. There was little, if any, anemia, but there was a definite slight megalocytosis.

Jessie S., the fourth member of the second generation, aged 53 years, was first seen at the Massachusetts General Hospital, April 5, 1916. She had been weak since the birth of her last child, 8 years previously, and since this time she had marked menorrhagia. There were exacerbations of weakness, and during one of these attacks she took Bland's pills and felt improved for 1 year. Examination showed pallor, but no jaundice. The tongue was atrophic and clean. Roentgen ray examination of the chest

showed enlargement of the heart, especially of the right side. The liver was felt 6 cm., and the spleen 3 cm., below the costal margin. There was edema of both lower legs. The knee jerks were normal, there was no ankle clonus and Babinski sign was negative. Laboratory findings: Red blood cells, 2,080,000 per e.mm.; hemoglobin, 35 per cent (Sahli); the red cells were achromic, there was marked variation in size and shape and some polychromatophilia; white blood cells, 2250 per e.mm.; neutrophils, 74 per cent; lymphocytes, 23; "transitionals," 3. The blood platelets were decreased. The Wassermann test was negative. Coagulation time was normal. Fragility test: Hemolysis began in 0.5 per cent and was not complete in 0.22 per cent sodium chlorid solution.

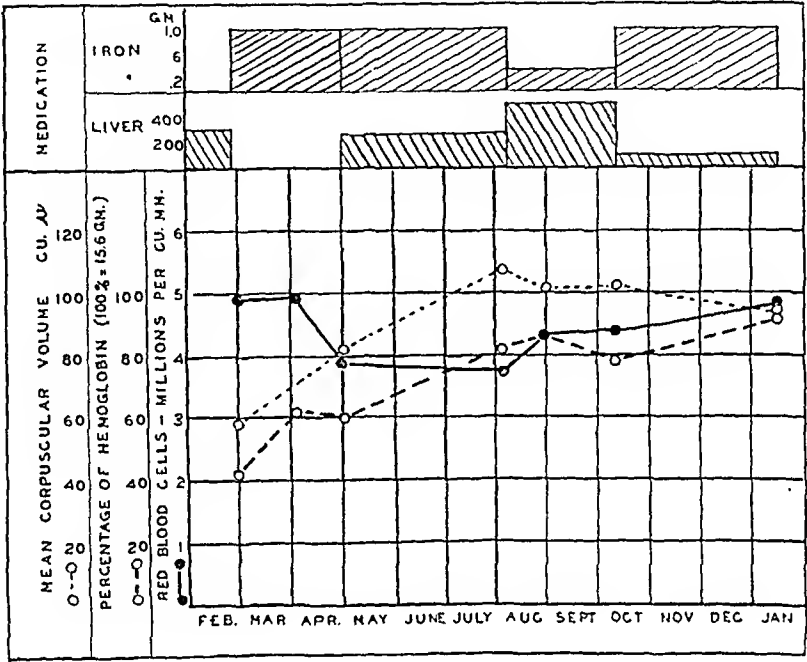


FIG. 1.—Changes in the blood of Jessie S. (See also Fig. 3.)

A dilatation and euretteage was performed and she was sent home to rest. She took 45 grains of Bland's pills a day for 3 months. Later she reported that she had had a year of good health, the best since her trouble began. She was not seen again until February, 1931. The following is a summary of the findings: She stated that the weakness and pallor had continued and generally in January of each year she had palpitation, dyspnea and a smothered feeling in the chest. Menorrhagia had continued up to the menopause, 5 years previously, which was produced by a series of Roentgen ray treatments. She had occasional "canker sores" of the tongue. Within a few months she had had prickly sensations of the fingers and especially of her feet when she stood, interfering to a small extent with her walking. She thought her nails had always tended to break easily. She was constipated. Three years previously, at a time when she was very weak, she was given a transfusion of blood. After this she took daily liver extract, No. 343 (N. N. R.), derived from 600 gm. of liver, for 2 or 3 months and was much improved. Following this, she took smaller amounts of liver extract irregularly, but for the last 3 months she had been taking daily the extract derived from 200 to 400 gm. of liver. At about the time of the transfusion she had

a very severe nosebleed. Her diet for many years had contained fruit only once every other day, one helping of vegetables a day and small helpings of meat 4 times a week. She drank about 6 cups of tea a day.

She had been married 30 years. Her husband died in 1931 of an "acute Landry's paralysis." She had 3 sons, aged 29, 26 and 23 years. She thought all had been well but considered that the eldest son had always been pale. A blood examination of this son by his physician, on May 22, 1928, was as follows: Red blood cells, 4,000,000 per c.mm.; hemoglobin, 85 per cent; white blood cells, 7000 per c.mm. One made on February 12, 1931, was reported: Red blood cells, 5,240,000 per c.mm.; hemoglobin, 96 per cent; white blood cells, 8100 per c.mm., "normal smear." The other 2 sons are reported upon below.

Physical examination revealed a well-developed and nourished woman with white-gray hair and light blue eyes. Tongue smooth with complete atrophy of the epithelium of the tip and edges. No lymph node enlargement. Thyroid gland moderately enlarged. Heart moderately enlarged. Blood pressure was 115 systolic and 65 diastolic. Lungs negative. Spleen felt 3 cm. below the costal margin. Liver not palpable. Reflexes: biceps jerks present and equal, knee and ankle jerks not obtained. Babinski sign doubtful, no ankle clonus, definitely diminished vibratory sense over both lower extremities. The finger nails showed a moderate degree of koilonychia.

Laboratory findings: (The red blood cells and hemoglobin are recorded in Table 2.) White blood cells, 9200 per c.mm.; neutrophils, 61 per cent; lymphocytes, 29; monocytes, 6; eosinophils, 2; basophils, 2. Smear: 1 normoblast seen; red cells seemed, on the average, small and very achromic and to have marked variation in size and shape (Fig. 3, a). Blood platelets increased. Fragility test: Hemolysis began in 0.54 per cent and complete in 0.18 per cent. Icteric index, 3. Gastric analysis showed no free hydrochloric acid 1 hour after histamin subcutaneously and peptic activity was nearly absent.

TABLE 2.—CASE OF JESSIE S.

Date.	R.b.c., millions per c.mm.	Hemo- globin, per cent.	Mean corpuscular volume, cu. micra.	Liver, and liver extract, No. 343, derived from liver. Grams daily.	Iron and ammonium citrate. Grams of iron daily.
Feb. 27*	4.89	42	58	0	1.0
April 3	4.91	61	..	0	1.0†
May 16	3.92	60	82	200-300	1.0
Aug. 6	3.86	81	107	500	0.3
Aug. 27	4.31	87	101	500	0.3
Oct. 17	4.38	79	101	100	1.0
Jan. 16	4.82	92	97		

* Two to four hundred grams of liver had been taken for 3 months before observation but no iron.

† Omitted for 2 weeks.

Under the medication indicated in the table she gradually improved in strength and feeling of wellbeing. The paresthesias of the extremities, however, remained about the same. The fragility of the red cells approached normal, as the blood improved. The mean corpuscular volume rose above normal as large cells well filled with hemoglobin appeared in the circulation (Fig. 3, b) and later fell nearly to normal.

Of significance in this case are the prolonged history of anemia and menorrhagia, achlorhydria, symptoms and signs of mild combined system

disease, diet not very satisfactory, tongue atrophic, koilonychia and splenomegaly. Furthermore, of interest is the fact that a microcytic type of anemia was transformed during the course of iron therapy to a macrocytic type of anemia, and that improvement had occurred in the past on either iron or liver therapy.

James M., the fifth member of the second generation, aged 52 years, white, married, policeman, was seen on May 16, 1931, but was unable to remain for more than a very short time, and thus the examination was not thorough. He had always been well and strong except for an occasional "cold." He had had no serious illnesses nor headaches. His tongue had never been sore (except that he stated that certain foods had sometimes produced "cankers"); he had no indigestion or gas; his bowels moved once a day. He had noticed no easy bleeding or bruising or brittleness of his nails, no paresthesias. At about 18 years of age he was subject to nosebleeds.

Physical examination: He was an extremely well-developed man with rather plethoric complexion, sparse, gray hair and light blue eyes. The tongue was not atrophic, although the extreme tip was reddened. His finger nails were normally strong and convex.

Blood examination: Red blood cells, 4,120,000 per c.mm.; hemoglobin, 89 per cent. The red cells appeared large. Mean corpuscular volume, 108 cu. micra (normal extremes, 85 to 95 cu. micra). There was much greater variation in the size of the red cells than normal with only slight variation in shape. No achromia. Fragility test: Hemolysis began in 0.5 and not complete in 0.18 per cent. White blood cells, 6450 per c.mm. Differential: neutrophils, 57.5 per cent; eosinophils, 1.5; basophils, 0.5; lymphocytes, 33.5; monocytes, 7. Blood platelets normal. Icteric index, 8.

He was seen again about 1 year later, at which time he still felt well and strong. Although advised to eat liver he had taken scarcely any. He had noticed at times, during the previous 9 months, a little numbness of the tips of the fingers, and practically constant slight numbness of the toes which had gradually spread over both feet. He had had no sore tongue, no diarrhea and no weakness.

Physical examination at this time revealed almost the same findings as before with the following additions: the heart, lungs and abdomen were negative; the spleen was not palpable; knee jerks and ankle jerks were present, but there was complete absence of vibratory sense over the left tibia; there were no other demonstrable deep or superficial sensory changes; the gait was normal.

The blood examination at this time was similar to the previous one: Red blood cells, 3,450,000 per c.mm.; hemoglobin, 95 per cent; mean corpuscular volume, 105 cu. micra. There was considerable variation in size of the red blood cells. Gastric analysis revealed the complete absence of free hydrochloric acid after histamin.

The symptoms and signs of early combined system disease, the megalocytic blood picture and the gastric achlorhydria led to the diagnosis of pernicious anemia in the case of this man.

Archie M., the sixth member of the second generation, aged 50 years, was living and well, married and had no children. He was said to be "in perfect health."

Annie M., the seventh member of the second generation, died 12 years previously, at the age of 35 years. Two years before her death she gave birth to a son. She never felt well thereafter and her health gradually declined. She had pallor, breathlessness, palpitation and developed a "lemon yellow color" to the skin. She was bedridden 2 months before her death. One month before her death "big, purple blotches on the legs" were noticed. She never mentioned her tongue being sore. She tended to be constipated and was never known to have any diarrhea. She

evidently died of an anemia, of what kind it would be difficult to say, presumably pernicious anemia.

John M., the eighth member of the second generation, died, in 1925, at the age of 40 years, of pulmonary tuberculosis. He had many hemorrhages from the lungs. He was said to have "high color" at the times when he was well and was not having hemorrhages.

Gertrude M., the ninth member of the second generation, aged 42 years, housewife, was seen in February, 1931. She was in good health up to 6 years previously when her feet "went back on her." She had trouble with walking, paresthesias of the hands and feet, and at the same time her tongue, cheeks and throat became sore. The doctor, she thought, said that her "blood was 2,000,000" and he advised bed rest for about 6 weeks. At this time she noticed that she had black and blue spots on very slight injury. During the past 6 years, in or about January, she had become weak, pale and had some breathlessness on exertion and a constricting feeling in her upper chest. She also frequently had a sore tongue. She began taking raw liver 5 years previously and for the past 3 years she had taken daily "a third of a pound" of liver and also liver extract, No. 343 (N. N. R.), derived from 200 gm. of liver, with considerable benefit. She stated that "for years" her finger nails broke easily. She had no diarrhea. Catamenia occurred monthly, lasting 3 to 4 days, requiring 4 to 5 pads a day. Her diet contained daily moderate amounts of fruit, vegetables and meat. For the past 6 years she ate red meat daily. Most of her life she took 8 cups of tea and 6 to 9 slices of bread a day.

She was married 21 years. Her husband was living and well, and her only child, a daughter, aged 20 years, was well, had no anemia and no disturbance of the menses. (See later, case of Ruth M.) The remainder of the history was negative.

Physical examination revealed a well developed and nourished woman, not obviously pale, with gray eyes, and brown-gray hair. Tongue smooth, atrophic and reddened. Thyroid gland moderately enlarged. No lymph node enlargement. Heart not enlarged. Blood pressure was 120 systolic and 80 diastolic. Lungs normal. Liver and spleen not palpable. Neurologic examination: Arm jerks equal and active; knee and ankle jerks not obtained; Babinski moderately positive response; absent ankle clonus; absent vibratory sense over the lower legs; Romberg test positive; gait moderately ataxic. The finger nails showed evidence of dystrophy.

Laboratory findings: (See Table 3 for red blood cells and hemoglobin.) White blood cells, 5200 per c.mm.; neutrophils, 52.5 per cent; lymphocytes, 37; monocytes, 7.5; eosinophils, 3. The red blood cells appeared on the average to be small and this was borne out by measurements. They were definitely achromic and varied markedly in size and shape. Blood platelets were present in normal numbers. Icteric index, 3. Fragility test: Hemolysis began at 0.48 and was complete in 0.16 per cent. Gastric analysis: No free hydrochloric acid 1 hour after histamin subcutaneously; peptic activity present but much diminished.

The patient improved slowly but very definitely upon the treatment indicated in Table 3. The mean corpuscular volume rose above normal during treatment, and a low color index was transformed to a high color index (Fig. 2). Paresthesias definitely diminished and she thought she could walk better, although to all appearances her ataxia was about the same.

The outstanding features of this case were the presence of combined system disease, achlorhydria, microcytic blood picture passing later to a macrocytic blood picture under the influence of iron. There was a reasonably satisfactory diet but one containing 8 cups of tea and a large amount of bread. There was abnormal fragility of the red blood cells, a history of easy bruising and koilonychia.

Fannie M., the tenth and last member of the second generation, was living and well in New York State. She was not known to be anemic. It was thought that there had been no trouble with her catamenia. She had 2 children who were perfectly well and not pale.

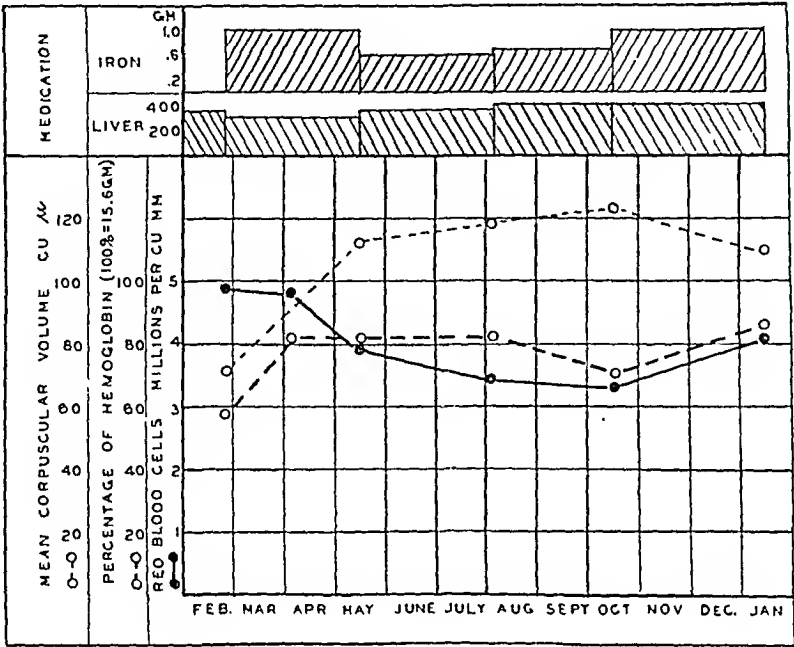


FIG. 2.—Changes in the blood of Gertrude M.

TABLE 3.—CASE OF GERTRUDE M.

Date.	R.b.c., millions per c.mm.	Hemo- globin, per cent.	Mean corpuscular volume, cu. micra.	Liver, and liver extract, No. 343. Grams daily.	Iron and ammonium citrate. Grams of iron daily.
Feb. 27*	4.93	57	71	250	1.0
April 3	4.81	81	...	250	1.0
May 16	3.81	81	112	400	0.6
Aug. 6	3.42	82	118	400	0.6
Oct. 17	3.25	69	123	400	1.0
Jan. 16	4.06	86	111		

* About 370 grams of liver were taken daily for 3 years before observation. No iron was taken.

Third Generation. Of this generation 5 have been examined and are reported here.

Hazel M. (second child of Elizabeth M.), aged 35 years, single, office worker, was seen briefly in May, 1931. She complained of a constant bloody vaginal discharge for 8 years. Menses began at 14 years, occurred monthly, lasted 6 days and were not profuse until 8 years previously, when she began to have a constant flow, usually somewhat bloody, requiring 1 pad a day, and a profuse flow of blood at the regular time of menstruation. Five years previously her uterus was curetted but without relief. Since

the onset of menorrhagia she had been troubled by dyspnea and palpitation, although she had not stopped work. One year previously, because her "metabolism test" was low, she began to take "6 thyroid tablets" a day. She thought these helped her strength, but she discontinued this therapy after several months. She never felt sensitive to cold or noticed loss of hair. She had gained 30 pounds in 3 or 4 years (present weight, 190 pounds). She stated that she bruised easily and that her finger nails broke easily. Her lips tended to crack easily. Her past history revealed nothing remarkable. Her hair turned gray when she was 25 years of age.

Physical examination revealed a rather obese woman with gray hair (not sparse) and light blue eyes. She was moderately pale. Her tongue was not atrophic; the tip was covered with large, smooth papillae. There were several large white scars in the fundus of the right eye, and the disc was slightly blurred. The fundus of the left eye was normal. The thyroid gland was not enlarged. The heart, lungs and abdomen were negative. Blood pressure was 100 systolic and 60 diastolic. Spleen not palpable. The reflexes were normal. There were a few ecchymoses on the thighs. There was moderate dystrophy of the finger nails.

Laboratory examination: Red blood cells, 5,060,000 per c.mm.; hemoglobin, 63 per cent. The red cells were small and achromic with moderate variation in size and marked variation in shape. Mean corpuscular volume, 74 cu. micra (normal extremes, 85 to 95 cu. micra). Fragility tests: Hemolysis began in 0.5 and was not complete in 0.18 per cent. White blood cells, 10,400 per c.mm.; neutrophils, 57 per cent; monocytes, 7.5; eosinophils, 2; basophils, 0.5. Blood increased. Icteric index, 5. Gastric analysis showed maximal free hydrochloric acid of only 18, 1 hour after histamin subcutaneously. The peptic activity was somewhat reduced.

She was ordered to take 6 gm. of iron and ammonium citrate daily, but because of diarrhea was able to take only 2 to 4 gm. Three months later the red blood cells were 4,960,000 per c.mm.; mean corpuscular volume, 84 cu. micra; hemoglobin, 80 per cent. She felt improved in strength. The pronounced metrorrhagia had ceased, but the amount of menstrual flow was still increased. Eight months after the start of iron therapy she reported that she had had normal menses for several months, although she was troubled somewhat by leucorrhea. The red blood cells were 5,390,000; mean corpuscular volume, 89 cu. micra; hemoglobin, 96 per cent.

This case is interesting from the following standpoints: Menorrhagia, which was present also in the patient's mother and was relieved during the course of iron therapy, easy bruising, dystrophy of the nails and a microcytic blood picture which, in sharp contrast to the other cases, did not become macrocytic under iron treatment.

Gertrude M. (youngest daughter of Elizabeth M.) was seen, August 30, 1931. She was 28 years of age, single, clerk, who felt strong and well up to a year previously. During the past year she had a little recurrent pain in the right upper quadrant, with "bilious attacks." She thought that at these times her color became slightly yellow. She never noticed light-colored stools or dark urine. Eight years previously she had a swelling in the neck which was thought to be "goiter." She was treated by her doctor with biweekly internal throat applications of iodine for 6 months, after which the swelling subsided. Her diet had always been rich in fruit, vegetables and red meat. She never had a sore tongue, paresthesias or diarrhea. Her periods were scanty and came about every 5 weeks. Her finger nails seemed to be brittle. She never noticed easy bruising.

Physical examination revealed a girl of normal appearance, with brown hair and blue eyes. Tongue not atrophic. Thyroid gland palpable but

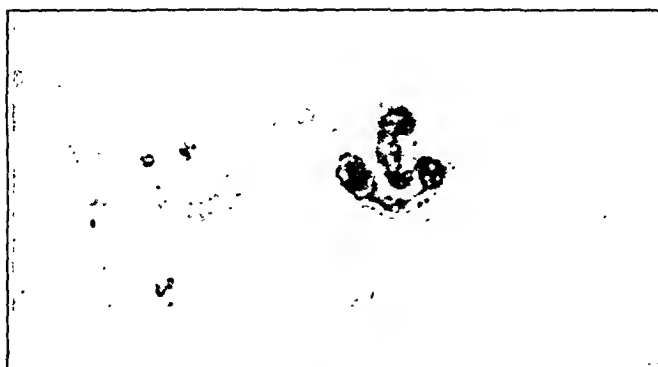


FIG. 3a

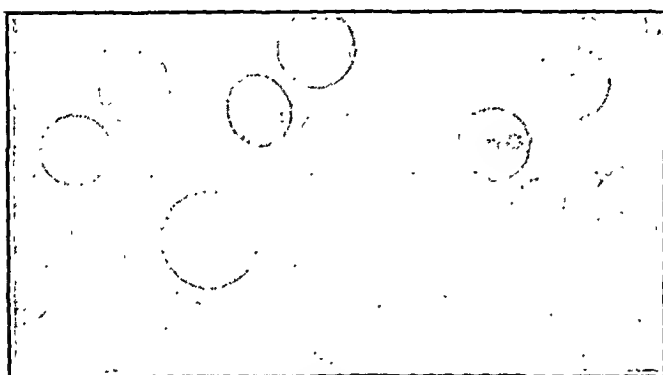


FIG. 3b

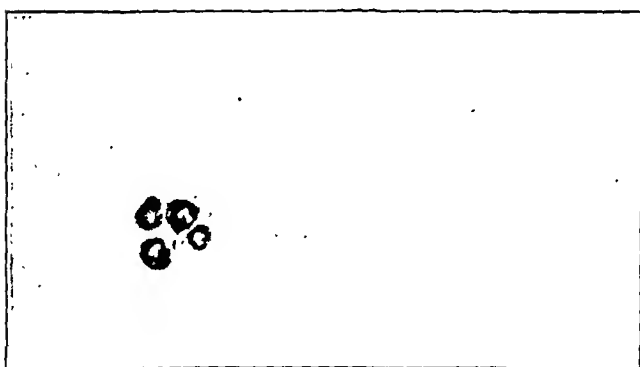


FIG. 3c

FIG. 3a, b and c.—Photomicrographs ($\times 1500$) of blood smears on Jessie S., at different stages of treatment. Data given in Table 2; 3a = February, 27; 3b = May, 16; 3c = August, 27.

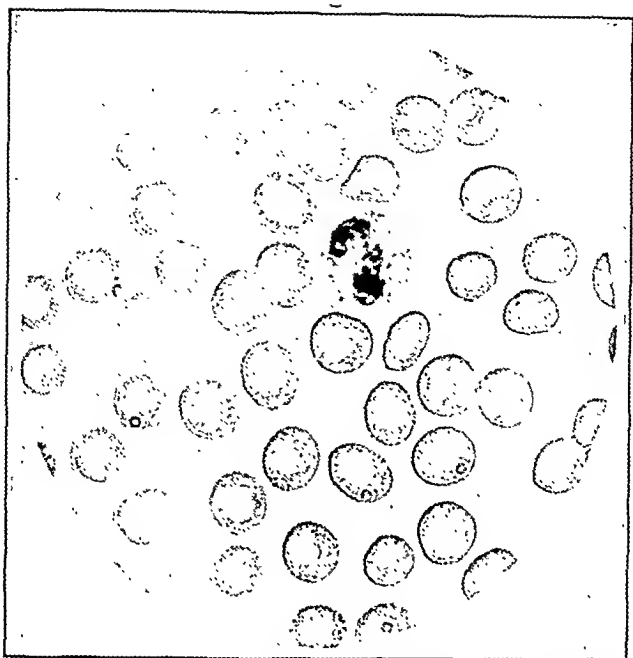


FIG. 4a.—Photomicrograph of blood smear on Allen S. (son of Jessie S.) ($\times 1500$). Red blood cells, 4,310,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume, 106 cu. micra.

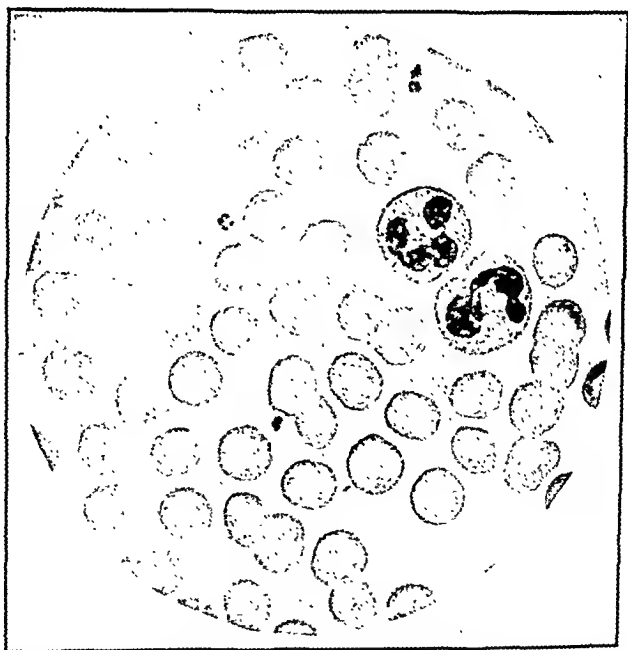


FIG. 4b.—Photomicrograph of blood smear on a normal man for comparison ($\times 1500$). Red blood cells, 5,100,000 per c.mm.; hemoglobin, 91 per cent; mean corpuscular volume 81 cu. micra.

not enlarged. Reflexes normal. No definite evidence of dystrophy of the nails.

Blood examination: Red blood cells, 4,720,000 per c.mm.; hemoglobin, 82 per cent. The red cells appeared normal in size and showed very moderate variation in shape. They were not achromic. Mean corpuscular volume, 88 cu. micra. Fragility test: Hemolysis began at 0.46 and was complete at 0.3 per cent. White blood cells, 10,400 per c.mm.; neutrophils, 65 per cent; eosinophils, 0.5; basophils, 1.5; lymphocytes, 24; monocytes, 9. The blood platelets were normal.

Gastric analysis revealed a normal amount of free hydrochloric acid 20 minutes after histamin.

Of note in this case were the history of gastrointestinal and thyroid gland disturbance and the very slight changes in the red blood cells.

Malcolm S. (the second child of Jessie S.) was seen on September 17, 1931. He was 26 years of age, single, draftsman. He had always been in good health and had had no serious illnesses. For 3 years he had suffered from headaches, usually left-sided, sometimes accompanied by scotomata, often occurring on Sundays. He had had no sore tongue, diarrhea or paresthesias and no history suggesting anemia.

Physical examination showed a well-developed and nourished young man with dark brown and sparse hair and gray eyes. Skin showed a few lesions of psoriasis on the scalp and legs. Tongue not atrophic; thyroid gland not enlarged. Heart, lungs and abdomen negative. Reflexes normal.

Laboratory findings: Red blood cells, 4,450,000 per c.mm.; hemoglobin, 90 per cent. The red cells showed a very slight but definitely increased variation in size and shape. Mean corpuscular volume, 99 cu. micra. The fragility of the red corpuscles was within normal limits. Count of the white blood cells, 6000; neutrophils, 51.5 per cent; eosinophils, 0.5; basophils, 0.5; lymphocytes, 34; monocytes, 13.5. These examinations were repeated and the findings confirmed 3 months later. Free hydrochloric acid was present in the gastric contents in normal amount.

Important findings: Increased mean corpuscular volume and slight variation in size and shape of the red blood cells, in the presence of no obvious anemia and normal gastric analysis; mild migraine.

Allan S. (youngest son of Jessie S.), aged 23 years, single, hosiery factory worker, was seen on August 6, 1931. He was considered always to have been in perfect health. He never had a sore tongue or intestinal disturbances. His appetite was good and he had always eaten a generous diet of a wide variety of food. His tongue appeared normal. He had dark brown hair and blue eyes. His finger nails were normal. There was a fine tremor of the hands. The thyroid gland was moderately enlarged. The spleen was not palpable. Reflexes were normal and vibratory sense undiminished over the tibiae.

Laboratory findings: Red blood cell, 4,310,000 per c.mm.; hemoglobin, 91 per cent. The red cells appeared somewhat large but only rarely was there seen either a large or rather small red blood cell (Fig. 4). Mean corpuscular volume, 102 cu. micra (normal extremes, 85 to 95 cu. micra). Fragility test: Hemolysis began at 0.46 and was complete at 0.26 per cent. White blood cells, 6800 per c.mm.; neutrophils, 47 per cent; eosinophils, 2; basophils, 2; lymphocytes, 40; monocytes, 9. Blood platelets present in normal numbers. A blood examination 3 weeks later showed red blood cells, 4,140,000; hemoglobin, 91 per cent; mean corpuscular volume, 106 cu. micra. Gastric analysis showed normal free hydrochloric acid.

Important findings: There was an increased mean corpuscular volume and slight changes in the red cells on examination of the blood film, but no definite anemia and normal gastric juice. The thyroid gland was enlarged.

Ruth M. (only child of Gertrude M.), aged 21 years, single, office worker. She felt strong and had been considered to be in perfect health with the exception of dysmenorrhea, which had not been incapacitating. She had had no menorrhagia and had no symptoms of anemia. Her diet had always been moderately reduced in vegetables and meat. Her paternal grandmother, residing in Detroit, was said to have pernicious anemia and difficulty in walking, and was improving under suitable therapy.

Physical examination showed a somewhat obese girl of a normal appearance with brown-black hair and gray eyes. Tongue not atrophic. Thyroid gland not enlarged. Heart, lungs and abdomen normal. Reflexes normal.

Laboratory findings: Red blood cells, 4,330,000 per c.mm.; hemoglobin, 84 per cent; the red blood cells appeared normal in size and shape. Mean corpuscular volume, 87 cu. micra. Fragility test: Hemolysis began at 0.46 and was complete at 0.28 per cent. White blood cells, 9700; neutrophils, 49.5 per cent; eosinophils, 2; basophils, 2; lymphocytes, 34.5; monocytes, 12. Blood platelets present in normal numbers. Gastric analysis showed free hydrochloric acid present in normal quantity.

This girl appeared to be in normal health but her family history was unusual.

Discussion. Table 1 summarizes the outstanding facts concerning this family. Attention is called to the presence of cholecystitis, migraine and an enlarged thyroid gland in several of the members; but it is not intended here to discuss their relationship to the familial anemia which may quite possibly exist. Neuburger³⁸ described a patient with pernicious anemia who had enlargement of the thyroid gland, and whose mother and daughter also had thyroid enlargement. Meulengracht,³⁹ on the basis of 8 cases, believed that there was a relationship between pernicious anemia and Basedow's disease.

From various points of view, one can plausibly consider that both pernicious anemia and idiopathic hypochromic anemia occurred in each of 3 sisters of the second generation, namely, Elizabeth M., Jessie S. and Gertrude M. Elizabeth M. and Jessie S., in 1916, and Jessie S. and Gertrude M., in 1931, had anemia with a low color index. Elizabeth M., in 1922, was demonstrated to have a high color index and, in 1931, combined system disease and, although then no definite anemia, a color index of a little over 1 and slight poikilocytosis—a picture compatible with pernicious anemia with combined system disease in partial remission. Jessie S. also had combined system disease in 1931, but at this time she had a severe hypochromic anemia. She had been taking liver extract. Under the administration of iron the red blood cells became megalocytic until the anemia was at length abolished by liver and iron therapy, and then the red blood cells became normocytic. Gertrude M. showed, when first seen, a hypochromic anemia with advanced combined system disease. She also had been taking liver extract. This was continued, but under the administration of iron her blood went through changes similar to those of Jessie S. Both sisters had great symptomatic improvement. Tables 2 and 3 and Figs. 1, 2

and 3 illustrate these changes. It is interesting that the red blood cell count fell in both cases when iron was first given. The explanation for this lies in the fact that the newly formed red blood cells had a much larger content of hemoglobin than formerly. (Fig. 3, *b*, which shows several macrocytes well filled with hemoglobin.) Other patients with idiopathic hypochromic anemia with achlorhydria but without evidence of a pernicious anemia element, when given iron, have not developed macrocytosis. In pure idiopathic hypochromic anemia there is presumably no lack of stroma-building substance.

Each of these 3 sisters had achlorhydria. It is noteworthy that in their cases the combined system disease had been very slowly progressive, which is apparently true also of their brother, James M. The anemia appears also to have been on the whole very slowly progressive. Menorrhagia occurs in about 20 per cent of cases of idiopathic hypochromic anemia with achlorhydria and may intensify the anemia. Easy bruising and dystrophy of the nails are also common in severe idiopathic hypochromic anemia. An enlarged spleen is found occasionally in both types of anemia and a history of an undesirable diet occurs frequently in both types. It is probably both a result of and a contributing factor to the anemia.

The fragility tests of the red blood corpuscles in these sisters showed a slightly decreased minimal and a pronounced increased maximal resistance, that is to say, an increased resistance span. Such an increased span has been described by Hill⁴⁰ in pernicious and hypochromic anemia, by Waugh⁴¹ in hypochromic anemia, by Minot and Buckman⁴² in erythremia and has been studied by Minot²¹ in various conditions. It is not characteristic of familial hemolytic jaundice which shows a decreased minimal and maximal resistance. Moreover, the return of the fragility of the red blood cells to normal limits, as the anemia improved under liver and iron therapy, is also not characteristic of familial hemolytic jaundice.

The ease of Hazel M., daughter of Elizabeth M., is characteristic of idiopathic hypochromic anemia, with reduced free hydrochloric acid in the gastric contents. She was completely alleviated by iron therapy alone. In her case there is, as yet, no evidence of pernicious anemia.

The presence of a hypochromic blood picture in the female members of the family, and its absence in the male members, is a fact worthy of emphasis. That this is not coincidence is shown by the fact that in other similar families recorded in the literature the hypochromic anemia occurs particularly in females and is rare in males. These facts, together with the occurrence of chlorosis in girls and rarely in boys, still await explanation.

The presence of a megalocytic blood picture in the 2 sons of Jessie S. (Fig. 4 and Table 1), without anemia and without reduction in gastric free hydrochloric acid, is at first sight exceedingly perplex-

ing. However, Castle and his coworkers¹ have definitely proven that absence of free hydrochloric acid is not a *sine qua non* of pernicious anemia. Moreover, appreciable amounts of the gastric specific factor have been found in a few cases of pernicious anemia, having free hydrochloric acid present in the gastric contents.^{1,43} It is very probable that in these 2 young men there is some reduction in the specific factor of the stomach secretion, and that one is witnessing here an extremely early form of pernicious anemia in younger members of a family in which the disease has a very slowly progressive character. Such a megalocytosis without definite anemia has been reported in members of pernicious anemia families by Todd¹⁶ and others. Allan M., the uncle of the 2 boys, may be considered to have a further advanced stage of the disease with nearly complete absence of free hydrochloric acid and probably a greater reduction in the gastric specific factor. His disease has taken a form in which a lower bowel disturbance is predominant, as is not unusual early in pernicious anemia.

It is believed that in this family there is an inherited tendency to reduce gastric function, which is responsible for the different types of anemia. There is much proof of a direct causal relationship between diminished gastric secretion and pernicious anemia. In general, the increasing evidence of the relationship of disturbances of the gastrointestinal tract to anemia⁴⁴ leads to suspect such a relationship in idiopathic hypochromic anemia.³ The presence of hypochromic anemia in members of a family and, moreover, its presence in individual members who also have pernicious anemia are indicative of a similar causal relationship. This also helps to clarify the belief that idiopathic hypochromic anemia is primarily the result of a deficiency, conditioned by a disorder of the gastrointestinal tract which leads to an inability to absorb or utilize hemoglobin-building material from the food.

Summary and Conclusions. 1. The literature reveals abundant evidence to prove an interrelationship between pernicious anemia and idiopathic hypochromic anemia, and their common relation to disorders of the gastrointestinal tract, exemplified by achlorhydria.

2. A family is reported in which pernicious anemia and idiopathic hypochromic anemia with achlorhydria were both present in each of 3 sisters. The histories and blood findings of other members of the family were suggestive of borderline anemic states, while several had either pernicious anemia or hypochromic anemia.

3. By analogy with the well-corroborated hypothesis of Castle, that pernicious anemia is secondary to the absence of a specific factor in the stomach, it is believed that idiopathic hypochromic anemia is primarily the result of a deficiency, conditioned by a disorder of the gastrointestinal tract, leading to an inability to absorb or utilize hemoglobin-building material from the food.

NOTE.—I am indebted to Miss Geneva A. Daland for the tests of the fragility of the red blood cells as well as for other technical data given in this paper.

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ERYTHROCYTES IN PELLAGRA.

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A REINVESTIGATION of the erythrocytes of pellagrins, using the most accurate methods now available, seemed to be indicated on account of the existence of many similarities between pellagra and

pernicious anemia. Our results are reported, although they confirm previous work done with less accurate methods. The extensive literature on the blood picture of pellagra has been thoroughly reviewed by Huck,¹ who also made studies of 20 patients. He found that other observers reported that in uncomplicated pellagra there may be no anemia or it may be present in a mild, moderate or severe degree and be of the chlorotic or secondary type. All of Huck's patients showed secondary anemia. Mollow and Klein,² in Bulgaria, in an extensive study of the blood cells of pellagrins, found the anemia always of the secondary type except for 1 patient who, after suffering from recurrent pellagra for many years, finally showed the blood picture, as well as the clinical features, of pernicious anemia.

Methods and Standards of Accuracy. Venous blood was drawn into a clean, dry syringe, using as little stasis as possible, and placed in a 15 by 150 mm. test tube. It was defibrinated with a small dry glass rod and kept stoppered to prevent evaporation. All samples were taken after a 12-hour abstinence from food; intake of fluids was not limited. The hemocytometer and diluting pipettes used were certified by the United States Bureau of Standards. The erythrocyte count reported was the average of two or more, usually three, estimations which agreed within 200,000 cells. Each estimation involved the use of a clean, dry diluting pipette and a clean, dry hemocytometer. Parallel erythrocyte counts were made on a series of bloods, using both oxalated and defibrinated specimens of the same blood and no appreciable differences were noted. The hematocrit tube, 100 mm. deep, described by Wintrobe³ and used in his later studies, was used throughout. Of course, no correction for shrinkage was necessary since no anticoagulant was used. The Newcomer method for hemoglobin was employed, the glass disk carefully standardized by Dr. Wintrobe being used.

The group of 50 pellagrins whom we have studied was made up of 39 colored women, 7 white women and 4 white men. In none of them was the diagnosis doubtful. The age of our pellagrins by decades was as follows: (1) 1; (2) 4, 1 below the age of puberty; (3) 16; (4) 17; (5) 7; (6) 5.

In the main, the patients were studied without selection as they were admitted to the hospital. However, for a few weeks admissions were so frequent that not all could be studied and choice was made of those who had skin lesions of shortest duration. Some were omitted because of complications, such as stricture of the rectum, although a few of these cases were included. Eighty per cent showed or gave history of glossitis; 50 per cent exhibited serious mental symptoms during their stay in the hospital. Of the 31 whose gastric analyses were done 10 showed the presence of hydrochloric acid and 21 showed its absence. Twenty-nine of the 50 patients left the hospital as improved, 6 as unimproved and 15 (30 per cent) died while in the hospital. Six patients told of previous attacks of pellagra, while the others were apparently in the first attack. It is of some interest that only 1 of the 6 cases with a history of previous attacks showed definite anemia. There were 29 patients (58 per cent) who had shown skin lesions for 1 month or less and 12 (24 per cent) for 2 weeks or less; 3 developed the dermatitis while in the ward. Since these patients are hospital bed patients, they surely represent in the main examples of severe pellagra. This is supported by the high death rate.

Using the same technique and procedure, 21 healthy young men (medical students) were studied.

The standards for normal are given in the first lines in Table 1. These

values are in the main from Wintrobe's review.⁴ In some instances the range of normal values has been extended to include results of our study of healthy men. It will be noted that the average hemoglobin value for normals for both men and women is 15.5 gm. (104 per cent), while the average for young men is 16.2 gm. (112 per cent). It seems rather extraordinary that the average hemoglobin value for normal individuals should have a value of greater than 100 per cent. This is due to the fact that the value represented by 100 per cent hemoglobin, 14.5 gm., is based on the average hemoglobin content of healthy individuals calculated to a red cell count of 5,000,000. Since the average normal red cell count is greater than 5,000,000, the average hemoglobin content is greater than the accepted standard for 100 per cent. This confusing maneuver is necessary in order to preserve the traditional color index which demands that 100 per cent represent the hemoglobin content of a normal blood which has a cell count of 5,000,000, which is less than the normal average count. The necessity for such an artificial standard in order to maintain the usefulness of the color index emphasizes the need for more rational factors which will express characteristics of erythrocytes in absolute values. Probably the most useful characteristic of red cells which may be expressed by a figure is the average size, preferably stated as volume. The method of calculation of the average volume of erythrocytes in cubic micra from known red cell count and hematocrit readings was introduced by Haden,⁵ who pointed out the value of such calculations in the study of anemia. However, Haden⁶ prefers to express average corpuscular volume in terms of per cent of normal, i. e., by the volume index of Capps.⁷ Wintrobe⁸ has advocated the custom of expressing the characteristics of erythrocytes in absolute values rather than relative to normal. Since the size of the normal red blood cell is a range rather than an exact level and on account of considerations mentioned above, Wintrobe's position seems quite sound. The two other useful characteristics of red blood cells which may be expressed in absolute rather than relative units are, according to Wintrobe's terminology:⁸ mean corpuscular hemoglobin and corpuscular hemoglobin concentration.

In the cursory statistical analysis of our data we have used the results of only the first study of each patient in order to avoid distortion due to the repeated studies made on a few patients with marked anemia. One exception to this rule will be noted in Fig. 3, where 69 observations were used. As to the degree of anemia, the 50 pellagrins were grouped as follows: Without anemia, i. e., with more than 12 gm. of hemoglobin per 100 cc., there were 28 patients (56 per cent); with slight or questionable anemia, 10 to 12 gm. hemoglobin per 100 cc., 8 patients (16 per cent); with moderate anemia, 8 to 10 gm. of hemoglobin, 6 patients (12 per cent) and extremely severe anemia, less than 6 gm. of hemoglobin, 2 patients (4 per cent). Of the 15 patients who died 10 showed no anemia, while 3 showed severe and 2 moderate anemia. By inspection of the histograms of Fig. 1 and the graph in Fig. 2 it will be noted that the size of erythrocytes of our pellagrins was with one exception either within the normal range or smaller than normal. In only 1 instance did mean corpuscular volume exceed 100 cubic micra and that was only 103 cubic micra. The erythrocytes showing the classic picture of pernicious anemia have

TABLE 1.—DATA FOR 50 CASES OF TYPICAL PELLAGRA AND 1 CASE OF SPRUE RESEMBLING PELLAGRA.

Case.	Age.	Sex.	Color.	Interval since previous study.	Recent diarrhea.	Duration of dermatitis.	Glossitis.	Psychosis.	Free HCl, stomach.	Condition at discharge.	R.b.c., millions.	% r.b.c. hematocrit.	Hemoglobin, gm. per 100 cc.	Hemoglobin %.	Corpuscular volume, cu. miera.	Mean corpuscular, hemoglobin $\gamma\gamma$ (10 ⁻¹² gm.).	Corpuscular hemoglobin concentration %.	Volume index.	Color index.	Saturation index.	Remarks.	
																						Maximum } Values Mean } for Minimum } normal.
1	33	F	C	10 D	+	4 D	+	0	0	1	7.30	56.0	20.0	130	100	31.5	30.0	1.20	1.20	1.25		
2	37	F	C	4 D	0	2 M	+	0	0	1	5.50	43.0	16.2	112	83	28.5	35.0	0.95	0.97	1.02		
3	33	F	W	21 D	0	3 Y/6 M 1 W	+	0	0	1	4.40	31.0	11.5	79	70	26.5	33.0	0.73	0.80	0.80		
4	37	F	C	21 D	0	6 M	+	0	0	1	2.87	14.9	5.59	39	52	19.5	37.5	0.61	0.68	1.11	Luetic proctitis.	
5	21	F	C	2 D	0	2 D	+	0	0	1	1.92	10.7	3.92	27	45	16.6	36.7	0.58	0.58	1.05	Luetic ulcers of leg.	
6	31	F	C	3 D	0	3 M	+	0	0	1	1.88	11.9	4.40	30	63	23.4	31.7	0.65	0.66	0.97	Second attack.	
7	28	F	C	3 D	0	3 M	+	0	0	1	4.11	23.1	7.30	51	56	17.8	31.6	0.67	0.63	0.94	Ovarian cyst; salpin-	
8	21	F	C	7 D	0	3 W	+	0	0	1	3.55	22.7	8.05	56	60	19.6	32.5	0.73	0.68	0.91	gitis.	
9	21	F	C	3 D	0	4 M	+	0	0	1	5.47	37.3	10.96	76	61	24.6	32.9	0.76	0.77	1.01	Congenital aphyllitis.	
10	33	F	C	3 D	0	4 M	+	0	0	1	6.06	38.3	13.30	93	63	22.0	34.7	0.76	0.77	1.01		
11	30	F	C	3 M	0	4 M	+	0	0	1	5.51	33.5	12.66	88	61	23.0	37.8	0.72	0.80	1.11	Tuberculous perito-	
12	28	F	C	3 M	0	3 W	+	0	0	1	6.54	41.7	14.74	102	64	22.6	35.4	0.77	0.79	1.03	ritis.	
13	35	F	C	3 W	0	3 W	+	0	0	1	4.36	35.2	14.10	98	80	32.4	32.4	0.97	1.14	1.18	Luetic proctitis with	
14	36	F	C	3 D	0	3 D	+	0	0	1	3.85	24.9	7.81	55	65	19.8	31.5	0.78	0.71	0.91	stricture terminal.	
15	36	F	C	3 W	0	3 W	+	0	0	1	4.73	31.3	8.90	63	66	18.8	28.4	0.78	0.66	0.85	Imbecile.	
16	32	F	C	10 D	0	3 W	+	0	0	1	3.93	25.0	7.81	55	66	19.9	30.2	0.80	0.70	0.87	Partial obstruction of	
17	24	F	C	22 D	0	4 M	+	0	0	1	5.76	38.6	13.50	94	67	23.4	35.0	0.81	0.82	0.99	cecum.	
18	21	F	C	7 D	0	3 W	+	0	0	1	6.51	41.5	15.75	109	68	24.2	35.4	0.83	0.82	1.01	Stricture of cecum.	
19	40	F	C	7 D	0	3 W	+	0	0	1	5.99	39.9	13.30	93	69	22.3	33.4	0.80	0.77	0.96		
20	29	F	C	7 D	0	2 W	+	0	0	1	4.79	32.8	12.46	87	69	20.0	38.0	0.82	0.91	1.11		
					0	3 W	+	0	0	1	3.49	24.3	7.60	53	70	21.8	31.3	0.83	0.76	0.92		
					0	3 W	+	0	0	1	3.50	23.0	9.10	63	66	26.0	30.6	0.79	0.90	1.14		
					0	3 W	+	0	0	1	3.01	23.3	7.81	55	77	25.8	35.6	0.93	0.90	0.97		
					0	3 W	+	0	0	1	5.57	36.9	14.53	101	71	26.1	36.4	0.80	0.91	1.14		
					0	3 W	+	0	0	1	6.95	42.7	14.53	101	71	26.1	36.4	0.80	0.91	1.14		
					0	3 W	+	0	0	1	4.79	33.5	11.80	82	71	24.6	31.9	0.84	0.86	1.02		
					0	3 W	+	0	0	1	5.08	36.5	13.30	93	70	26.2	37.5	0.83	0.91	1.10		
					0	3 W	+	0	0	1	5.01	36.1	12.00	84	72	23.8	38.6	0.87	0.83	0.98	Vomiting; postopera-	

a mean corpuscular volume of from 110 to 150 cubic micra. Anemia when present was definitely of the normocytic or microcytic type and not of the macrocytic type.

As to how richly the erythrocytes are supplied with hemoglobin, the histogram in Fig. 1 shows that 34 per cent of the patients had a corpuscular hemoglobin concentration below the normal range, while 66 per cent were within the normal range. Haden⁵ and Wintrobe⁹ found subnormal concentration of corpuscular hemoglobin characteristic of secondary anemias due to chronic loss of blood. Only 7 of the 17 patients showing this type of cells showed

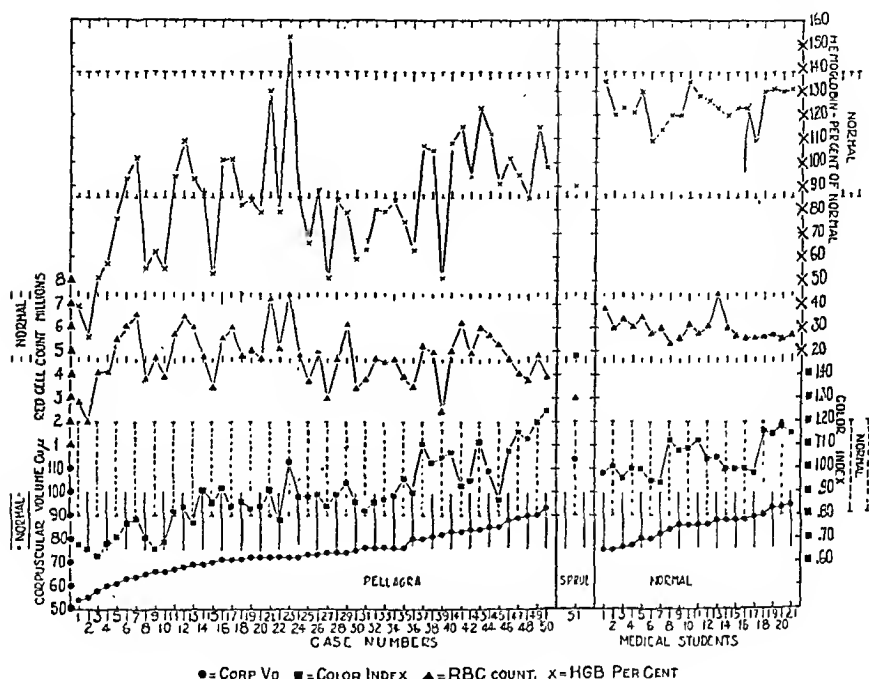
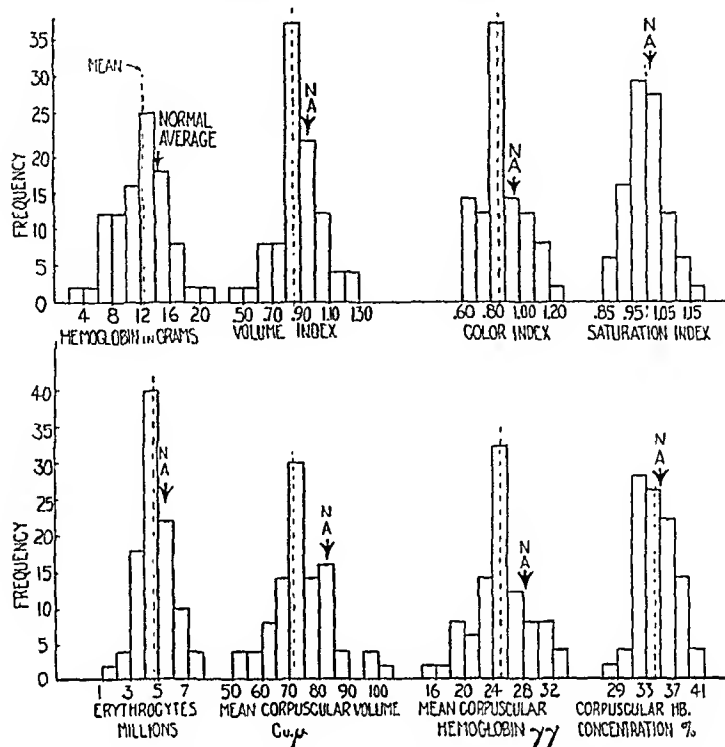


Fig. 1.—Data recorded are for first study on each of 50 typical pellagrins; 1 patient with sprue resembled pellagra clinically; and 21 healthy medical students. Same routine and technique used for all. One hundred per cent hemoglobin = 14.5 gm. per 100 cc.

clinical evidences of chronic blood loss. Among the 33 patients with normal concentration of hemoglobin in the red cells were 2 with extremely severe anemia and 7 others with slight anemia. All but 3 of the 17 patients with low corpuscular hemoglobin concentration had anemia of varying grade as indicated by hemoglobin content in grams per 100 cc. of blood. Therefore of the 24 patients with anemia of varying degree, 10 had erythrocytes with the normal concentration of hemoglobin, while 14 had cells containing less hemoglobin than their size demanded.

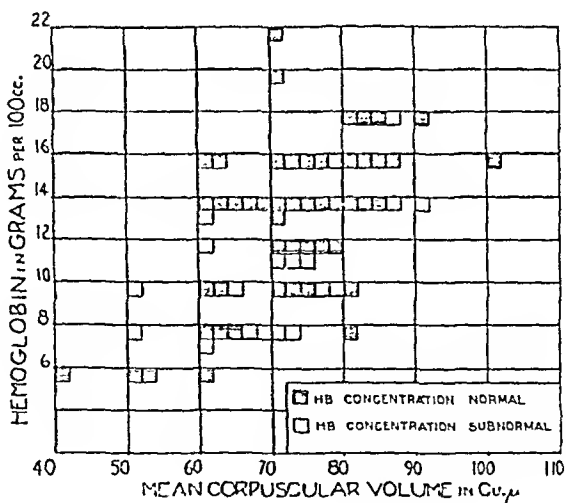
Examination of Fig. 3 will show that there was a relationship

FIG. 2.—FREQUENCY DISTRIBUTION OF VARIATION OF VARIOUS VALUES FOR 50 BLOODS FROM 50 PELLAGRINS.



Dotted lines show the means. NA = the normal average.

FIG. 3.—CORRELATION BETWEEN HEMOGLOBIN CONTENT OF BLOOD AND AVERAGE VOLUME OF THE RED CELLS (BASED ON 69 SPECIMENS OF BLOOD FROM 50 PATIENTS WITH PELLAGRA).



The distribution of bloods containing cells with subnormal concentration of hemoglobin is also shown. Each square represents one specimen of blood. Correlation coefficient = $+0.526 \pm 0.0059$.

between degree of anemia as measured by the hemoglobin content of the blood and size of the cells; patients with normal hemoglobin values usually had red cells of normal average volume, while those whose hemoglobin was less than normal usually had cells also smaller than normal, and roughly proportional to the hemoglobin level, expressed in grams per 100 cc., the correlation coefficient being $+0.526 \pm 0.0059$. This is in striking contrast with the blood of pernicious anemia. In this disease, as is well known, when anemia becomes more severe and hemoglobin content of the blood falls, the average volume of the red cells increases to far above the normal value.*

For a number of pellagrins the cells were smaller than normal though the red cell counts were not low. Fig. 3 shows the distribution of bloods made up of pale cells, that is, with less than the normal concentration of hemoglobin. Such cells were noted about as frequently in those with moderate anemia as in severe anemia.

Case 51 illustrates the possible value of the erythrocytic picture in the diagnosis of pellagra. This patient did not speak English and a satisfactory history was not obtained until several days after admission. He had a severe diarrhea and a sore tongue; his hands and feet showed desquamation of the skin with slight pigmentation. The affected areas did not show sharply defined borders, however. His erythrocytes were of the macrocytic type. In the differential diagnosis on admission pellagra occupied a prominent position. He later gave the history that his hands and feet had been edematous 1 month before and he was obviously suffering from arteriosclerotic heart disease with congestive failure which was no doubt aggravated by the anemia. The previously existing edema was thought to explain the skin lesions. His stools were frothy and bulky, and his gastric contents contained free hydrochloric acid. He was free of abnormal mental symptoms. His condition was called sprue rather than pellagra. The response to liver therapy tended to confirm that diagnosis.

A number of influences have been considered as possibly having a bearing upon the degree and type of anemia present in pellagra. It is interesting to note that of the 8 patients who showed a severe or extremely severe anemia 5 had other diseases, such as syphilis or organic intestinal disease, which might have played an important part in the production of anemia. One patient (Case 36), not included in the above 8, suffered from uncomplicated pellagra. She had 9.1 gm. of hemoglobin per 100 cc. of blood on admission, and 3 weeks later 6.65 gm. During this time there was considerable loss of blood from extensive ulcerated, but not obviously infected,

* A personal communication from Dr. M. M. Wintrobe, to whom I am greatly indebted, is as follows: "The coefficient of correlation between hemoglobin in grams and mean corpuscular volume for 657 determinations in pernicious anemia is -0.4960 ± 0.0294 ."

skin lesions. During the interval considerable dehydration had probably been overcome, which may have played an important part in the change in hemoglobin concentration of the blood. Intestinal parasites have not appeared to play an important part in the production of anemia in the group studied. It has been suggested by several observers that anemia of pellagra is dependent upon the presence of diarrhea, upon the loss of iron and other blood-building constituents by the bowel. The average hemoglobin content of the blood of 17 patients who had not suffered from diarrhea differed by less than 1 per cent from the average for 25 who had been suffering from diarrhea. Two patients with diarrhea whose hemoglobin percentages were very high, due apparently to dehydration, were excluded from these calculations. Concentration of the blood due to loss of body fluids may have been a factor in obscuring anemia in others of these patients. Determinations of circulating blood volume¹⁰ carried out since the observations reported here were made have shown that the total quantity of erythrocytes in pellagra may frequently show more striking diminution than is indicated by hemoglobin or hematocrit readings. This is due to diminished plasma volume. It is probable that a greater absolute anemia existed, particularly in some of our patients who died, than the hemoglobin values indicated. The tendency toward high red cell counts and hemoglobin content noted in some of the normal young men in our series may also have been due to mild dehydration, since the specimens were taken early in the morning and before they had eaten breakfast.

Many of our patients gave most unsatisfactory histories concerning their diet. Among those thought to be reliable a number had taken regularly a diet containing fresh lean meat. Others, and the majority, had eaten little or no lean meat. Many had taken an abundance of fresh green vegetables. No difference in the degree or type of anemia could be detected in those whose diet was obviously faulty and those who had taken a fairly satisfactory diet. Also, there were no obvious differences in the blood pictures of those with achylia and those whose gastric contents contained free hydrochloric acid.

Many physicians have noticed and recorded the striking similarities existing between pernicious anemia and pellagra, especially of symptomatology and morbid anatomy. The proof within recent years of the beneficial effects of diet in pernicious anemia has suggested possible parallelism also in the matter of pathogenesis, particularly since foods which are hematopoietic in pernicious anemia are highly recommended for the pellagrin. The most characteristic single easily demonstrable abnormality of the patient with pernicious anemia is the macrocytic anemia. The contrasting tendency for anemia in pellagra to be normocytic or microcytic would seem to indicate a definite and significant difference in

pathogenesis in the two diseases, however much they may have in common.

Bliss¹¹ has suggested that iron deficiency might be the cause of pellagra. The demonstration that many pellagrins, particularly during the early stages of the disease, do not show anemia, does not support his hypothesis.

Summary. 1. Using the most accurate available methods, erythrocyte counts and determinations of hemoglobin and percentages of packed red cells have been made for 70 bloods from 50 patients with typical pellagra. The results with the calculated mean corpuscular volume, mean corpuscular hemoglobin, corpuscular hemoglobin concentration, volume index, color index and saturation index along with certain clinical features are reported in Table 1. The data for 1 case of sprue which might have been considered pellagra are included in the table.

2. In a graph the blood pictures of the 50 pellagrins are contrasted with those of 21 medical students and that of a case of sprue. In other graphs results are further analyzed.

3. Of the pellagrins 56 per cent showed no appreciable anemia; 16 per cent slight or questionable anemia; 12 per cent showed moderate anemia and 12 per cent a severe anemia, while 4 per cent showed an extremely severe anemia.

4. Two-thirds of the patients who died showed no anemia according to the methods and standards used.

5. Among those with severe anemia, other diseases which might have caused anemia were common.

6. Patients who suffered from diarrhea did not appear to be more anemic than those without diarrhea.

7. The influence of dehydration in obscuring anemia is discussed.

8. Anemia, when present, was definitely of the chlorotic, normocytic, or microcytic type, and in no instance of the macrocytic type.

9. Of the pellagrins 34 per cent had erythrocytes with corpuscular hemoglobin concentration less than normal, while for 66 per cent the concentration was within the normal range.

10. The average size of the red cells tended to diminish in proportion to the severity of the anemia, contrasting with the opposite rule for pernicious anemia.

11. The importance of the blood picture in the differential diagnosis between pellagra and pernicious anemia or sprue is emphasized.

NOTE.—We wish to record our gratitude to the late Dr. J. Birney Guthrie, through whose kindness and interest we had the privilege of studying the colored women pellagrins in this series. Throughout the study his keen enthusiasm for the investigation of pellagra was felt.

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THE NONFILAMENT POLYMORPHONUCLEAR NEUTROPHIL COUNT IN TYPHOID AND UNDULANT FEVER.

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SINCE the classification of the polymorphonuclear neutrophilic leukocytes by Arneth,¹ in 1904, there has been a gradual increase in our knowledge regarding their function. The development of the Schilling¹⁰ index furnished a larger number of investigators with a more simple means of enumerating the various forms of polymorphonuclear neutrophils, and subsequent studies by Pons and Krumbhaar,⁹ Cooke and Ponder,² Piney,⁸ Farley, St. Clair and Reisinger,³ and others have provided even the most inexperienced worker with efficient and practical methods.

The method suggested by Farley *et al.* is based on a simplification of the Cooke and Ponder classification of the polymorphonuclear neutrophils and is especially designed for routine clinical use. In this method the polymorphonuclear neutrophils are divided into two groups, the first being identical with Cooke and Ponder's Class I and the other group including their other four classes. The groups are designated by Farley as "nonfilament polymorphonuclears" and "filament polymorphonuclears," respectively. The nonfilament group includes those young or immature cells whose nuclear material is connected by broad bands; the filament group comprises older cells whose segments of nuclear material are joined by fine filaments. On the basis of 100 presumably normal adults, Farley *et al.* suggest 16 per cent nonfilament cells as the upper limit of

normal, and 8 per cent as the average. Medlar⁶ regards as abnormal a nonfilament count higher than 8 per cent.

The value of such studies is becoming widely recognized. Arneth¹ and Cooke and Ponder² and many others have reported the increase of immature forms in acute infections; Goodale and Manning⁵ have emphasized the supplementary value of the Schilling index in the diagnosis of acute appendicitis; Mullin and Large⁷ found that the nonfilament count follows the course of the infection more closely than does the total leukocyte count; Farley *et al.*³ and Weiss^{11,12} have emphasized the value of the method in determining the degree of bone marrow response to infection and shown that the actual degree of bone marrow response may be reflected in the number of immature cells but not in the total leukocyte count.

The present report is concerned with the nonfilament neutrophil count in two diseases which are usually associated with leukopenia. The majority of the counts were made on the day of admission of the patient to the hospital. The day of the disease is, of course, only an estimation. Since leukopenia is regarded as associated with either an inhibition of the bone marrow by bacterial or other toxins, or with an increased destruction of the leukocytes, study of the nonfilament forms in these diseases should indicate whether their leukopenia is a result of bone marrow inhibition or of excessive white blood cell destruction. However, a disturbance of a leukopoietic mechanism which governed cell maturation, such as has been hypothesized by Fitz-Hugh and Krumbhaar⁴ in agranulocytic angina, might result in an increase in the number of young forms present. The differential counts in the following table were made according to the method outlined by Farley *et al.*³ The total percentage of polymorphonuclear leukocytes is the sum of the non-filament and filament groups.

Comment. It is obvious that in practically every instance there has been a striking increase in the number of nonfilament forms. In only 2 of the cases of typhoid fever was the initial percentage of nonfilament forms less than 20, and in 11 of the cases it was over 30. The percentage of nonfilament forms in the 2 cases of undulant fever was also markedly increased. In 4 of the cases of typhoid fever there was a moderate leukocytosis which was transitory in 2 instances and probably caused by a bacterial invasion of some tissues other than those of the gastrointestinal tract. The conception of myeloid tissue depression or nonreactivity to stimulation, which is generally offered as explanation of the leukopenia in typhoid fever, does not seem tenable in the presence of the high percentage of young polymorphonuclear cells. In view of the marked and progressive leukopenia the counts in Case J. A. are particularly interesting. This patient was very ill and, were only the total white blood count considered, it would have been said that his infection had overwhelmed the bone marrow. During the early days of his

illness that statement would not have been justified by the nonfilament count; and even in the third week the bone marrow responded well, although not as actively as previously. The patient recovered.

TABLE I.—FILAMENT AND NONFILAMENT AND DIFFERENTIAL COUNTS (100 CELLS EACH).

Case.	Day of disease.	White blood count.	Nonfilament polys.	Filament polys.	Lymphos.	Monos.	Eosinos.	Basos.
TYPHOID FEVER.								
C. E.	9	9,500	60	21	18	1	0	0
	16	5,500	29	29	42	0	0	0
R. R.	12	4,300	20	66	14	0	0	0
R. D.	7	5,100	20	60	18	2	0	0
J. D.	13	6,300	36	24	36	4	0	0
F. A.	16	7,300	38	50	12	0	0	0
I. L.	8	5,200	28	30	42	0	0	0
I. K.	14	13,000	36	32	32	0	0	0
	30	8,000	35	30	35	0	0	0
E. L.	9	6,250	13	55	20	12	0	0
J. M.	12	11,500	58	21	17	3	1	0
W. T.	4	6,600	20	52	26	2	0	0
	7	3,200	56	32	10	2	0	0
C. A.	11	6,050	36	28	24	12	0	0
M. S.	6	4,100	30	39	24	7	0	0
A. S.	12	6,600	31	45	15	8	1	0
V. S.	8	11,200	46	25	24	5	0	0
A. C.	8	4,800	64	8	26	2	0	0
S. P.	17	4,050	24	50	16	10	0	0
J. A.	4	3,400	55	13	24	7	1	0
	10	1,950	34	15	49	2	0	0
	17	2,900	8	12	80	0	0	0
	18	3,200	16	26	58	0	0	0
UNDULANT FEVER.								
E. G.	20	4,850	34	14	48	4	0	0
O. I.	14	4,200	52	30	16	2	0	0

The increase in the nonfilament count in the majority of these cases indicates that the leukopoietic system is responding to severe demands by furnishing immature cells, and suggests that it is a destruction of the white blood cells which is resulting in the leukopenia. In the presence of an increase in the nonfilament forms it does not seem logical to hypothecate that the leukopenia is associated with an inhibition of bone marrow function, but this increase may be due to a disturbance of a mechanism concerned with cell maturation.

Summary. 1. Total white blood cell counts and nonfilament polymorphonuclear neutrophil counts are recorded in 17 cases of typhoid fever and in 2 cases of undulant fever. These show a striking increase in the number of nonfilament, or immature, forms in the majority of instances.

2. The value of the nonfilament form count in the estimation of bone marrow response in these diseases is emphasized.

3. The suggestion is made that the increase in the nonfilament form of polymorphonuclear neutrophilic leukocyte is evidence that the leukopenia in these diseases is associated with white blood cell destruction rather than with bone marrow inhibition; but attention is directed to the possibility that the increase in the number of young forms present may be a result of a bone marrow disturbance which inhibits the maturation of the neutrophils.

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FURTHER NOTE ON A CASE OF GONORRHEAL ENDOCARDITIS WITH RECOVERY.

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IN 1930 I¹ reported a case of gonorrheal endocarditis with recovery. The endocarditis began February 17, 1928; the patient was discharged as recovered May 30, 1928. In view of the rarity of recovery in this condition further observations of this patient are deemed worthy of record.

The patient was again seen and examined September 1, 1931. He gave the following history: On his discharge he returned to his home in North Dakota where he attempted little in the way of

physical exertion for 3 months. During this time he gained in strength and at the end of the period he felt quite well. He found that his ability to exercise was normal: he was able to dance, swim, play golf and tramp without heart consciousness or abnormal sensations of any kind. He indulged freely in these exercises. He returned to Washington, D. C., July 14, 1931, weighing 148 pounds. Ten days later he began a lobar pneumonia of the left lower lobe which lasted 5 days, with 2 weeks' convalescence. He lost 16 pounds in weight during this illness. He gradually regained his strength and, when seen September 1, 1931, looked and seemed well.

Examination on this date showed the left border of cardiac dullness in the fifth interspace to be 9 cm., the right border of dullness in the fourth interspace to be 3 cm. Manubrial dullness in the second interspace was $5\frac{1}{2}$ cm. The pulse rate at the apex was 88. The rhythm of the heart was regular, the sounds clear, with the first apical slightly accentuated. At the base the aortic second sound was greater than the pulmonic, but neither was accentuated. In a well localized area in the second interspace at the left of the sternum there was a diastolic murmur which was maximum in the first half of diastole. It could be heard but faintly in the third interspace on the left. In the erect position the murmur distinctly decreased in intensity. The blood pressure was 118 systolic and 80 diastolic.

An electrocardiogram revealed a regular rhythm of a rate of 90 to 100, with *T* waves upright in all leads. The auriculoventricular and intraventricular conduction times were normal. There was slight slurring and notching of the *Q-R-S* complexes in Leads II and III. No axis deviation was shown. A 6-foot film of the heart gave the following measurements: M L, $8\frac{1}{2}$ cm.; M R, $4\frac{1}{2}$ cm.; transverse diameter of the chest, 30 cm.; diameter of the great vessels, 5 cm.

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BUNDLE BRANCH BLOCK; AN ANALYSIS OF 395 CASES.

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AFTER its origin, the cardiac impulse successively traverses the lower parts of the sinoauricular node, the auricular musculature,

the auriculoventricular node, His' bundle and its branches, and the Purkinje network, to reach the ventricular muscle fibers. Disturbances of conduction in each of the above tissues from the sinoauricular node to the Purkinje tissue inclusive, have been described. This paper deals with a series of cases in which electrocardiograms show what is interpreted as an interference with conduction in one of the large divisions of the bundle of His. Especial attention has been given to a "follow-up" study to determine the prognosis in these cases.

Since the early work of Eppinger and Rothberger,^{1,2} Lewis^{3,4} and Carter⁵ there have been many clinical and experimental studies which have extended our knowledge of this condition, 2 of which deserve particular mention.

In 1920 Wilson and Hermann⁶ critically reviewed the literature on bundle branch block and reported their own experiments relating to delayed conduction through the bundle branch divisions. They produced right bundle branch block in dogs by cutting the right branch of the His bundle, and then stimulated the right ventricle by single induction shocks. When the stimulus fell between *T* and the following *P*, a typical right ventricular extrasystole was obtained; when the stimulus fell during the latter part of the *P-R* interval or on the first part of *Q-R-S*, the complexes obtained were transitional in form between the extrasystolic complexes and the right bundle branch complexes. These complexes had *Q-R-S* intervals intermediate between those of normal curves and bundle-branch block curves, and *T* deflections transitional in type between those of normal deflection and those seen in bundle branch block. They also reported clinical observations on cases in which there was similar delay of conduction through the bundle branch divisions.

In 1929 Barker, MacLeod, Alexander and Wilson⁷ gave confirmation to earlier works^{8,9} which purported to show that what had previously been described as right bundle branch block was, in reality, left bundle branch block. In a human heart exposed by pericardiostomy and employing a technique similar to that used by Lewis, various points on the surface of the ventricles were electrically stimulated and the extrasystoles were simultaneously recorded by the usual three electrocardiographic leads. All of the curves from the right ventricle had upward initial deflections in Lead 1 and all those from the left ventricle had downward initial deflections in Lead 1. The change in direction was found to be produced by crossing the interventricular septum and not merely by a more lateral position. They also observed that as the superior aspect of the heart was approached the ventricular complexes in Leads 2 and 3 tended to become higher and toward the inferior aspect they became inverted. The only conclusion was to infer that curves obtained from the right ventricle were of the type previously supposed to be of left ventricular origin, and conversely curves formerly interpreted

as those of right bundle branch block were in reality those of left bundle branch block.

Review of Present Series. Selection of Cases. In reviewing over 16,000 electrocardiograms taken in the cardiac clinic of the Massachusetts General Hospital from January, 1915, to February, 1929, we have selected 395 as representing defective conduction through the bundle branches. This work represents an extension of that previously reported in 1923 by White and Viko.¹¹

Of these cases 69 per cent were semicharity patients on the general wards or were seen in the outpatient department, while 31 per cent were private patients. The 395 electrocardiograms include those of typical complete bundle branch block, and those transitional in form between complete block and normal conduction, which we believe represent partial block in the bundle branches. Furthermore, we are convinced from a review of recent literature that what has heretofore been called left bundle branch block is in reality right bundle branch block and *vice versa*. With these considerations in mind we have outlined the following classification.

Classification. IA. LEFT BUNDLE BRANCH BLOCK—HOMOPHASIC TYPE; so called because the *Q-R-S* complex and *T* wave have the same direction in Lead 1. This group fulfills all the criteria of complete left bundle branch block except that the *T* wave and *Q-R-S* complex are similarly directed in Lead 1.

IB. LEFT BUNDLE BRANCH BLOCK—HETEROPHASIC TYPE. In contrast to IA, the *Q-R-S* complex and *T* wave in this group are oppositely directed in Lead 1. The curves in this group fulfill all the classical criteria of complete left bundle branch block.

II. RIGHT BUNDLE BRANCH BLOCK—HETEROPHASIC TYPE. These curves fulfill all the classical criteria of complete right bundle branch block. There were no instances of right bundle branch block with similarly directed *Q-R-S* complexes and *T* waves (homophasic) in Lead 1.

III. BUNDLE BRANCH BLOCK—INTERMEDIATE TYPE. This group fulfills most of the classical criteria of complete bundle branch block. The *Q-R-S* is slurred and over 0.1 second in duration. The *T* wave is often but not always oppositely directed from the *Q-R-S* complex. The *Q-R-S* complexes are often similarly directed in Leads 1 and 3, but in no case are they absolutely typical of complete bundle branch block. These curves have been interpreted as partial bundle branch block with conduction sufficiently delayed to result in a *Q-R-S* complex of over 0.1 second in duration.

IV. SIGNIFICANT ABERRATION OF THE VENTRICULAR COMPLEXES (PROBABLY INDICATING SLIGHT DEGREES OF INTRAVENTRICULAR BUNDLE BRANCH BLOCK). The *Q-R-S* wave is usually slurred and notched but its duration is slightly if at all prolonged beyond normal limits. The *T* wave direction is variable. This group is probably the

early transitional type in which the delay is not marked. That it is associated with serious pathology is evident from the fact that the prognosis in these cases is no better than that in complete bundle branch block.

Cases of marked axis deviation which often give electrocardiograms resembling bundle branch block, have been excluded, as have cases of "functional bundle branch block."

The various data have been compiled separately for each division of the classification and also for the series as a whole, the intention being to make note of any significant differences between the various groups.

Distribution of Cases. Of the 395 cases, 125 were in Group I (26 in IA, 99 in IB), 29 in II, 81 in III and 160 in Group IV. It was possible to "follow" 308 cases (77 per cent) of which 223 (72 per cent of the 308 followed cases) were found to be dead and 85 alive.

Sex: 301 (76 per cent) were males, and 94 (24 per cent) were females; the sex ratio in the 5 groups was essentially similar.

Age: the age in 360 cases was known. Table 1 shows the age distribution in the 4 groups.

TABLE 1.—AGE DISTRIBUTION OF BUNDLE BRANCH BLOCK CASES.

Years.	IA.	IB.	II.	III.	IV.	Total.
0-9	0	0	0	0	1	1
10-19	0	0	1	5	0	6
20-29	0	4	1	3	6	14
30-39	3	4	3	6	6	22
40-49	2	18	5	8	25	58
50-59	9	25	5	25	51	115
60-69	8	23	6	16	48	101
70-79	2	15	3	11	9	40
80-on	0	0	1	1	1	3
	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>
	24	89				
Total	113		25	75	147	360

Etiology. While in only a few instances of bundle branch block have localized pathologic lesions been looked for, yet it is generally assumed that the etiology is usually an organic and not a functional disturbance of conduction. This appears true chiefly because this phenomenon is found almost exclusively in old diseased hearts. The cases of functional and intermittent block mentioned above are few in number and such cases are not included in this series. Consequently under etiology of the heart disease in our cases we have put the various factors commonly held to be responsible for heart disease, without the certainty that such disease in any individual instance was responsible for the conduction defect.

In 328 instances a note regarding etiology was made in the record; the results are summarized in Table 2.

TABLE 2.—ETIOLOGICAL FACTORS.

	Left bundle branch block.		Right bundle branch block.	Indeterminate bundle branch block.	Significant aberration.	Total.
	IA.	IB.	II.	III.	IV.	
Probable coronary arteriosclerosis	21	65	16	46	90	238
Hypertension	14	43	14	31	52	154
Rheumatism	1	13	6	12	15	47
Syphilis	4	1	6	13	24
Myxedema	1	1
Subacute bacterial endocarditis	1	1	2
Congenital heart disease	1	1
Chronic pericarditis	5	6	11
"Chronic myocarditis"	2	3	8
Acute pericarditis	1	1
Aneurysm of aorta	2	2

Associated Conditions. Pulse Rate. In 23 patients the heart rate was under 50 and in 8 of these it was under 40. In 93 instances the rate was above 90 but in only 5 instances was the heart rate above 120.

Arrhythmias. Table 3 shows the occurrence of associated electrocardiographic abnormalities; they occurred as frequently in patients with partial bundle branch block as in those with complete bundle branch block. The instances of pulsus alternans and gallop rhythm (where such note was made) are included in this table.

TABLE 3.—INCIDENCE OF ARRHYTHMIAS IN CASES OF BUNDLE BRANCH BLOCK.

	IA.	IB.	II.	III.	IV.	Total.
Ventricular premature beats	1	16	2	9	17	45
Auricular premature beats	1	7	4	1	4	16
Sinoauricular tachycardia	1	1	2	4
Auricular fibrillation	2	14	2	13	23	54
Auricular flutter	2	..	2
Paroxysmal auricular tachycardia	1	1	2
Paroxysmal ventricular tachycardia	1	..	2	1	4
Auricular standstill	1	1
Partial A-V block	1	4	3	3	9	20
Complete A-V block	2	2	7	6	..	17
Gallop rhythm	4	2	6
Pulsus alternans	5	..	1	3	9
Ventricular escape	1	2	3
S. A. bradycardia and ventricular escape	1

Structural Cardiac Defects. The heart size was noted in the records of 166 patients. The heart was enlarged in 154 of these 166 patients, Roentgen ray confirming the observation in 145 instances. In 12 cases the heart was of normal size by Roentgen ray. Mitral stenosis was present in 35 patients and 36 showed mitral regurgitation; aortic stenosis was present in 11 and aortic regurgitation in 49. Thirty-one patients had definite coronary occlusion and 2 had aneurysm of the aorta.

Evidence of Functional Insufficiency. Congestive failure was present in 118 cases, angina pectoris in 59, Adams-Stokes syndrome in 12, cardiac asthma in 12, and effort syndrome in 4. Gallop rhythm was noted in 6 cases and pulsus alternans in 9, but these signs were rarely carefully searched for, as White¹¹ found bundle branch block in 38 per cent of a series of 100 cases of gallop rhythm.

Associated diseased conditions of other organs were those that might be expected in patients of this age group. The more common of these were upper respiratory infections, nephritis, diabetes, arthritis and prostatic disease, in that order of frequency.

Prognosis. The data discussed above were compiled from the clinic and private consultation records. Additional information especially regarding the details of death has not been easy to obtain in most instances, but we were at least able to determine whether the patient was alive or dead in 308 (77 per cent) of the cases.

The prognosis in this series is not that of block of the bundle branches but the prognosis of patients in whom such block was present. It is hard to evaluate the importance of such a disturbance when so many other variables in the way of cardiac and extracardiac disease are present. All we can report is the length of life after bundle branch block was discovered, and that it almost invariably indicates serious organic heart disease.

TABLE 4.—DURATION OF SYMPTOMS IN 308 CASES "FOLLOWED UP."

Group.	Cases.	Average duration of symptoms.	Average known duration of bundle branch block.
IA . . .	7 living	5 years, 10 mos.	2 years, 7 mos.
	15 fatal	4 years	3 years, 7 mos.
IB . . .	17 living	4 years, 1 mo.	3 years, 1 mo.
	58 fatal	4 years, 5 mos.	1 year, 2 mos.
II . . .	6 living	7 years, 2 mos.	2 years, 5 mos.
	13 fatal	3 years, 2 mos.	1 year, 2 mos.
III . . .	15 living	3 years, 11 mos.	2 years, 8 mos.
	53 fatal	5 years	1 year, 4 mos.
IV . . .	40 living	7 years, 1 mo.	3 years
	84 fatal	3 years, 6 mos.	11 mos.
Entire series	85 living	5 years, 10 mos.	2 years, 11 mos.
	223 fatal	4 years, 1 mo.	1 year, 2 mos.

Table 4 shows the number of cases in each group about whom it was possible to obtain follow-up data. It also shows the average

duration of cardiac symptoms and the average known duration of bundle branch block for both the living and the fatal cases. It should be pointed out that in Group IA the average duration of bundle branch block in the fatal cases would read 1 year and 9 months instead of 3 years and 7 months if 3 quite unusual cases were omitted, also in Group II the average duration of symptoms in living cases would be 3 years instead of 7 years and 2 months if 1 very unusual case were omitted. Otherwise there is a strikingly close similarity of prognosis in each of the 5 groups. From this study it can only be concluded, that as a sign of serious organic heart disease, partial block in one of the bundle branches is equally as serious as complete bundle branch block. The figures compiled for the series taken as a whole are also shown.

With few exceptions the patients still living are either seriously limited in their activity or are actually in some stage of cardiac decompensation. Among the fatal cases the chief cause of death, where this is known, has been, in nearly every instance, cardiac failure.

Summary and Conclusions. 1. An analysis is presented of 395 cases of bundle branch block studied in the cardiac laboratory and clinic of the Massachusetts General Hospital.

2. The diagnosis of bundle branch block can only be made with certainty by the use of the electrocardiograph.

3. From the standpoint of diagnosis and prognosis it is important to determine its presence in cardiac patients.

4. Bundle branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series after the discovery of the conduction fault was 1 year and 2 months but 85 other cases are still alive after an average of 2 years and 11 months following the discovery of the bundle branch block.

5. Partial bundle branch block must be regarded clinically as equally significant with complete bundle branch block, the prognosis in both being essentially the same.

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EVALUATION OF VARIOUS METHODS OF INVESTIGATING THE CIRCULATION IN THE LOWER EXTREMITIES.*

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THE importance of studying the circulation has been stressed in numerous contributions during the past few years. Information to be gathered from these studies may be usefully applied in various ways: (1) To detect the presence of impaired circulation early enough to overcome it and permit collateral circulation to develop; this would be of particular value to the diabetic who is notoriously susceptible to arterial changes and gangrene; (2) as a means of making more accurate diagnoses of vascular diseases and distinguishing the vasospastic from the occlusive forms of arterial disease, and (3) it may serve a double purpose when surgical treatment is being considered, not only as to its advisability but may be the final factor in deciding the site of amputation.

There are various methods of studying the circulation. Considerable information may be obtained by questioning the patient and by a physical examination. A history of cramps, coldness, numbness, pains and burning sensations, and a thorough examination of the legs and feet (searching for various lesions¹ such as red spots, scars, scar depressions, or small focal areas of gangrene, pallor, discoloration, coldness, evidences of trophic disturbances, palpation of the pulses, particularly the dorsalis pedis artery, and the presence of sclerosis) will give much information as to whether the circulation is deficient or not.

Some insist that information obtained by a careful examination is sufficient to make satisfactory conclusions of the condition of the circulation. Whether this is so remains to be seen. The objectives of our studies were twofold: first, to determine, if possible, the accuracy of the subjective and objective findings of the physical examination and, second, what can be reasonably expected from the various and more recent methods of studying the circulation.

One hundred and fifty patients were included in this series of studies. Most of them were diabetics. Some were referred for a report on the circulation because they presented clinical pictures suggesting vascular disease. A small group of patients who had no symptoms or signs of vascular disturbances were likewise included.

* Read before the Jefferson Medical College Society for Clinical Investigation, February 25, 1932.

In order to simplify matters and make comparative studies of the various methods, the entire series of patients was divided into two main groups: Series A: those who presumably had a normal circulation, and Series B: those patients who presented evidences of deficient circulation. There were 78 cases in Series A and 72 in Series B.

The following routine of studying the patients was carried out. Observations were made for the presence or absence of lesions, the degree of the dorsalis pedis artery pulsation and evidences of sclerosis, coldness, trophic disturbances, the condition of the veins, and a record of the symptoms usually met with in circulatory disturbances. Oscillometric readings were taken of the feet and legs and the reaction of the skin and capillaries to histamin were recorded at various levels of the feet, legs and lower thighs. These studies were carried out in every case included in the two series. Roentgen ray studies, when possible, were made. The vessels of the legs and feet were examined for evidences of calcification. The intradermal wheal test was performed on a small group of patients, and in some selected cases skin surface temperature readings were made. However, the latter two tests were not employed routinely in the studies. The sphygmotonomograph was not available when this investigation was started.

Time and space permit only a brief description of the technique of the various methods employed:

Methods. The *oscillometer* of Pachon² was first described in 1909. The apparatus is similar in principle to the sphygmomanometer. It consists of an hermetically sealed metallic box, containing an aneroid capsule, upon which rests the registering needle and an armlet or rubber cuff. The oscillations of the sensitive needle attached to the aneroid capsule will depend upon the site of the extremity studied and the condition of the vessels. To these may be added the condition of the collateral circulation and the blood pressure.

Studies upon normal subjects were carried out by Heitz³ and Samuels.⁴ They found that normal readings at the following sites are: thigh, 4 to 16; upper third of leg, 3 to 12; foot, 0.5 to 2.

The *histamin test* is based on the studies of Lewis⁵ on the capillaries and their reactions to various stimuli. The clinical application of Lewis' studies was suggested by Starr.⁶ When histamin in a weak solution of 1 to 1000 is inoculated into the skin, a series of reactions take place. These changes are of three types: (a) A local dilatation of the capillaries at the site of the trauma or inoculation; (b) an erythematous discoloration about the spot due to relaxation of the arterioles, and (c) the development of a wheal resulting from the outpouring of plasma through the walls of the vessels. Of these phenomena the most important is the wheal. Normally the wheal should make its appearance and be complete within 5 minutes. The flare likewise appears within 5 minutes. Both the wheal and flare usually become more intense and are more definite at the 10-minute observation. For details of this test and the proper interpretation of the findings, the works of Lewis and Starr are recommended. Takats⁷ suggested in a recent contribution that the histamin solution be injected intradermally in order to insure more uniform reactions.

Calorimetric methods of studying the circulation in the extremities are determined chiefly by studying the amount of heat loss in a given time and by skin temperature observations. The latter method is preferable. Brooks and Jostes⁸ suggested a method of studying the skin surface temperature by means of an electrical apparatus consisting of a thermocouple and a galvanometer. These principles were amplified and modified by Scott⁹ and McGlone,¹⁰ thereby giving us apparatuses which are more practical for clinical use. These instruments are particularly valuable in the differential diagnosis of arterial diseases and when decisions have to be made as to the advisability of surgical procedures to correct the impaired circulation and to determine what improvement may be expected from these operations. This method of study has been favorably commented upon by Allen and Smithwick,¹¹ Brown,¹² Adson,¹³ White¹⁴ and others.

In patients who have deficient circulation, the problem of arteriospasm or mechanical occlusion of the lumen must be solved. On such occasions *skin surface temperature studies* are exceedingly helpful. Readings are taken before and after nerve block. The pressor or vasoconstrictor stimuli may be blocked either by spinal or general anesthesia and local infiltration of the nerves to the parts about to be studied. When this is accomplished, there is normally a rise of several degrees, depending upon the type of anesthesia and room temperature. This reading is known as the vasodilatation level and suggests that the spasm of the vessels has been overcome. When the skin temperature fails to reach the normal level, we assume that there is some mechanical obstruction to the arterial circulation. The difference between the highest skin temperature after nerve block and the normal vasodilatation level is termed the "obstruction" or "occlusion" index.

The value of the occlusion index becomes apparent when we are considering ganglionectomy or ramisectomy. If, for example, there is no rise in the skin surface temperature after 20 to 30 minutes following nerve block, we may conclude that the benefits from this operation are so slight that the procedure is not indicated. However, if the occlusion is only partial and the index is about 2, this suggests that the deficiency of the circulation is probably due to vasospasm and that improvement of the circulation may be expected from surgery.

Intradermal injections of salt solution were employed by McClure and Aldrich¹⁶ as a means of studying edema. Cohen¹⁷ and Stern¹⁸ suggested this test for determining the efficiency of the circulation in arterial disturbances. Briefly, the technique is as follows: 0.2 cc. of 0.85 per cent salt solution is injected intradermally at various levels of the extremity. The wheals produced by these injections are observed until they disappear. The time required for absorption of the fluid is determined by palpation and not by visual judgment. Normally, the disappearance time is 60 minutes. Readings of 5 to 10 minutes for disappearance time are usually found in areas adjacent to gangrene and readings between 10 and 20 minutes suggest a deficient circulation.

Roentgen ray studies of the vessels consist of the usual flat-plate roentgenograms giving us information upon the condition of the arteries, particularly for evidences of calcification. This is discussed more fully hereinafter when evaluating the various methods.

Bloodvessel visualization by injection of opaque solutions into the larger arteries prior to the Roentgen ray examination has been employed by Greenbaum and Carnett.¹⁹ This method, a procedure requiring surgical technique, can only be done in a hospital, and its field of usefulness is too limited to warrant promiscuous employment.

The *sphygmotonograph* or recording sphygmomanometer is based upon the same principle as the oscillogometer. Simpson,²⁰ and Pearse and Morton²¹ were favorably impressed with it. They claim that it has the added advan-

tage of giving accurate and permanent records of the circulation. Unfortunately, this instrument was not available when our studies were being carried out. The author is in no position to compare it with the other methods of study.

Comment Upon Method of Grouping. Of the above mentioned methods of study, the oscillometer and histamin tests were carried out in every one of the 150 patients. The symptoms, physical signs, and a search for lesions were recorded. Roentgen ray examinations were made when possible.

The studies and observations of every case were so recorded that statistical data would be available after a sufficient number of patients had been investigated. The studies included a careful physical examination and the above mentioned oscillometer and histamin tests and Roentgen ray. This information was recorded upon a form illustrated below.

The studies were reviewed in each case and the decision of classifying them as deficient or of ample circulation function was made. The problem of grouping the patients into the two series was not difficult when the results of the tests were uniformly positive or negative, but there were occasions where all the tests did not tally. In these cases the decision rested with the final outcome of the case, that is, if the major tests indicated good circulatory function and gangrene developed in the patient under observation, he was classified in the pathologic group or Series B. Patients who showed evidences of good circulatory function with the tests, who had little or no symptoms and signs but showed calcification of the vessels through the Roentgen ray, were placed in Series A, the efficient circulatory group. This will be discussed in detail when evaluating the different methods.

Some of the case records of the two groups have been arranged in tabular form to illustrate the method of classifying the results of the studies.

The arrangement of Table 2 is self-explanatory. Six records of each series are depicted. The symptoms and signs are charted + when present or positive, ⊕ when doubtful or indefinite, and ○ when absent. When symptoms and signs were intense ++ was used. Under the column for veins, a single + indicated varicosities, and ++ was employed when thrombophlebitis was present. The same method was employed for charting results of the tests. Normal oscillometric readings and histamin reactions are indicated by ○. When the oscillometer gave subnormal readings or the reaction was delayed, suggesting deficient circulation, the + sign was used; ++ was recorded if the oscillometric readings were zero or if the histamin test showed marked delay.

Some of the records were included in the table to illustrate the difficulty which presents itself when attempting to classify them. As an example of this problem, consider Case B-6. The good pulse,

TABLE 1.—FORM OF RECORDING RESULTS OF THE TESTS AND EXAMINATION OF (A) NORMAL CIRCULATION FUNCTION AND (B) DEFICIENT CIRCULATION.

Record of Patient With Efficient Circulation: Series A.																													
No.: 13-A	Name: J. R.	Age: 51	Female		Blood pressure: 140/80																								
History:	Examination:		R.	L.	Lesions:	R.	L.																						
Cramps	Coldness		0	0	Red spots				0																				
Coldness	Pulsations:				Blebs				0																				
Numbness	Dorsalis pedis		Good		Scars				0																				
Pains	Popliteal				Scar depressions				0																				
Burning sensations	Femoral				Ulcerations				0																				
	Phlebitis; thrombophlebitis		+	+	Focal gangrene				0																				
	Sclerosis		0	0					0																				
Oscillometer Readings:*																													
	Leg.		Foot.		Histamin Reaction:†																								
	R.	L.	R.	L.	Right.		Left.																						
					2½'	5'	2½'	5'	10'																				
Pressure: 160	10	12	2	2																									
140																													
120	12	11	1½	2																									
100																													
80	8	6	1½	2																									
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					Foot																								
					Ankle																								
					Knee																								
					Thigh																								

Roentgen ray examination:
No evidences of calcification in the vessels of the legs or feet.

Roentgen ray examination:

No evidences of calcification in the vessels of the legs or feet.

absence of coldness to the part, and negative Roentgen ray findings would suggest that this record belongs to the nonpathologic group. However, the circulatory function tests, both the oscillogram and histamin, definitely pointed to a deficient circulation. The contradictory findings suggest that the decision would rest with the ultimate outcome of the condition of the leg and further search for more clinical data. Lesions were present on the leg. Gangrene subsequently developed and amputation had to be performed in order to combat the toxemia which was progressively getting worse. Examination of the vessels of the amputated limb showed advanced arterial disease, thereby proving that the tests for circulatory function were helpful in pointing out the existence of impaired circulation despite the negative Roentgen ray and the lack of physical findings.

In Cases A-75 and A-77, conditions were reversed. The Roentgen rays showed evidences of calcification, but the tests were negative on all counts. The clinical background was one of normal or efficient circulatory function. Such cases were listed in Series A because the evidence, despite the Roentgen ray finding of calcification, was decidedly in favor of good circulatory function.

Discussion of Results and Evaluation of the Tests.—The data obtained from the records of the two series of patients were arranged in tabular form for statistical purposes and comparison. This information can be studied in Table 3:

Oscillogram Readings. In the group with good circulatory function, the oscillogram readings of the legs were within normal limits in 76 of the 78 cases (97.4 per cent). In the feet, normal readings were observed in 56 cases (71.8 per cent) and in 22 cases (28.2 per cent) the readings were below normal.

In Series B (the pathologic group) 49 cases (68 per cent) had subnormal readings in the legs, and in 23 cases (32 per cent) the readings were normal. Readings of the feet showed that 65 cases (90.3 per cent) were below normal and only 7 cases (9.7 per cent) had normal figures.

Briefly, the oscillogram seems to have given satisfactory or acceptable results in the efficient group (76 out of 78 cases), but failed to maintain the satisfactory percentage in the pathologic group, where only 68 per cent of the cases showed subnormal readings.

The interpretation of the findings in the pathologic group demands some discussion. At first glance one may assume that the oscillogram has failed to give us accurate information, since only 68 per cent showed evidences of deficient circulation, and therefore should be discredited as a test for circulatory function. A survey was made of the remaining 32 per cent of the patients who had good oscillogram readings despite the fact that they were classified in the pathologic group. A majority of this group had an increased blood pressure. There were no references in the literature to guide

TABLE 2.—SHOWING SOME OF THE RECORDS IN SERIES A (EFFICIENT CIRCULATION) AND SERIES B (IMPAIRED GROUP).

Case No.	Name.	Age.	Sex.	Symptoms.				Physical examination.						Oscillometer.		Histamin.		Roentgen ray.	Blood pressure.		Diagnosis.
				Cramps.	Coldness.	Pain.	Numbness.	Burning.	Pulse.	Sclerosis.	Coldness.	Lesions.	Veins.	Legs.	Feet.	Legs.	Feet.		Systolic.	Diastolic.	
A-1 . . .	R. B.	62	F.	0	0	0	0	0	Pres.	0	0	0	0	0	0	0	0	134	88	Diabetes
A-14 . . .	E. L.	43	F.	+	0	0	⊕	0	Pres.	⊕	0	0	0	0	0	0	0	Neg.	142	80	Thyroid
A-29 . . .	R. K.	50	F.	0	0	0	0	0	Pres.	⊕	0	0	0	0	0	0	0	Neg.	130	80	Diabetes
A-26 . . .	C. W.	42	F.	0	+	0	0	0	Pres.	0	+	⊕	+	0	0	⊕	0	Sl. deposits	130	90	Diabetes
A-75 . . .	C. C.	50	M.	0	0	0	0	0	Good	0	0	0	0	0	0	0	0	Calcif.	150	80	Diabetes
A-77 . . .	R. J.	59	F.	0	0	0	0	0	Good	0	0	0	0	0	0	0	0	Calcif.	170	100	Diabetes
B-6 . . .	M. B.	48	M.	+	+	+	0	0	Good	0	+	+	+	+	+	+	+	Neg.	130	70	Diab.; gangr.
B-8 . . .	M. F.	58	F.	0	+	+	+	+	Good	+	+	+	+	+	+	+	+	Calcif.	170	98	Diab.; threat. gangr.
B-16 . . .	M. K.	61	F.	+	+	+	0	0	Abs.	+	+	+	+	+	+	+	+	Calcif.	140	76	Diab.; gangr.
B-34 . . .	L. S.	60	M.	0	0	0	0	0	Good	0	0	0	0	0	0	0	0	Calcif.	120	70	Diab.; gangr.
B-76 . . .	C. S.	54	M.	+	+	0	0	0	Abs.	+	+	+	+	+	+	+	0	Calcif.	140	78	Diabetes
B-56 . . .	M. Z.	60	M.	0	+	0	0	0	Dim.	+	+	+	+	+	+	+	+	Neg.	134	74	Diab.; threat. gangr.

0 = Negative or normal.
+ = Positive findings.
⊕ = Questionable or suggestive.

0 = Negative or normal.

+ = Positive findings.

⊕ = Questionable or suggestive.

Cases:	Showing Comparative Frequency of the Symptoms and Signs With the Results of the Various Tests.	Oscillometer.	Histamin.	Röntgen ray
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[illegible]

us upon the question, but in our experiences hypertensives usually gave high oseillometric readings, and it is quite possible that the increase in pressure sends the blood through with greater force and gives good readings despite pathologic changes in the arteries. However, this need not apply in every case because there were occasions where the oscillometer showed subnormal readings in patients who had hypertension.

Another factor for consideration is the influence of the collateral circulation upon the readings. Since the mechanism of the oscillometer is so arranged as to give us information upon the gross bloodflow and the rhythmic expansion and contraction of the vessels, it is only fair to assume that if a satisfactory collateral circulation has been established, we may get normal readings despite the presence of definite disease in some of the vessels. These facts are presented for consideration and may explain some of the failures of the test to conform with the clinical findings. Recently, de Takats²² mentioned the possibilities of the oscillometer in determining the existence of an attempt to produce adequate collateral circulation.

The value of the oscillometric readings in the feet will be considered separately. In Series A, the readings were normal in 56 cases (72 per cent) of the 78, and in the remaining 22 cases (28 per cent) they were subnormal. The 72 per cent normal readings in the feet seem to be rather disappointing when the figures are compared with the excellent record of 97 per cent normal readings of the legs in the same group, Series A. In the pathologic group, Series B, observations on the feet showed that 65 cases (90.3 per cent) of the 72 had subnormal readings.

How are we to explain the 28 per cent subnormal readings in the feet of the presumably normal group, Series A? Is it because the instrument fails to give satisfactory results when studying the circulation in the feet or is it possible that there are either anatomic differences in the circulation or that early pathologic changes are taking place without apparent or perceptible manifestations?

Attempting to settle this question, it may be pertinent to mention that the skin surface temperature of the toes and soles even under normal conditions is several degrees below the temperature of other parts of the body. This finding lends itself to the thought that there may be some anatomic condition as a result of which the circulation in the feet does not keep pace with other areas. This contention is further supported by the fact that the same discrepancy between the leg and foot percentages were noticed in the statistical studies of the histamin reaction.

To summarize the merits of the oseillometer, it is an instrument which measures the degree of pulsation of the vessels in that particular area. It removes the arbitrary personal equation when the presence or absence of a pulse is under consideration. It permits

us to confirm information of the circulation gathered by physical examination, which may be misleading in a certain percentage of the cases. It may indicate the establishment of a collateral circulation in a limb with definite disease of the vessels. Normal oscillometric readings are particularly significant when they confirm a negative clinical background, that is, absence of signs, normal histamin response, and a negative Roentgen ray. A diagnosis of an efficient circulation in such cases is warranted.

Low oscillometric or zero readings almost invariably point to some impairment of the circulation. This suspicion is further strengthened if the various symptoms and signs are present and the histamin test shows a retarded or delayed response. The oscillometer, however, does not help us in determining whether the deficiency in circulation is due to a spasm of the vessel or to mechanical causes.

Normal readings may be found in some cases where the evidence points to pathologic changes in the vessels. Hypertension and the existence of a sufficient collateral circulation are offered as possible explanations on such occasions.

Histamin Reactions. The results of this test on the legs was normal in 77 out of the 78 cases (98.7 per cent) in Group A (the series of normal patients). In the feet the results were not so satisfactory; 56 patients showed a normal reaction, a percentage of 71.8 per cent and in 22 cases (28.2 per cent) the reaction was delayed. In Series B, the pathologic group, 53 cases out of 72 had a delayed reaction and, in 19 cases, the reaction was normal (73.6 per cent and 26.4 per cent respectively).

The best results were obtained in the normal group. In the pathologic series a good response to histamin was found in 26.4 per cent of the cases. Again, the question of reliability of the test is raised. The same arguments hold true for the histamin test as were offered for the oscillometer, particularly the possibility of the establishment of a satisfactory collateral circulation. The fact that in 13 of the 19 patients the normal response to histamin was confirmed by normal oscillometric readings is sufficient argument against condemning these tests and against deciding that they fail to detect pathologic conditions. On the contrary, may we not assume that their results strongly suggest that an efficient collateral circulation has taken over the burden of supplying the tissues in these extremities?

The results of the histamin reaction when investigating the circulation in the feet showed practically the same percentage as those obtained with the oscillometer. The discussion of the discrepancies of the oscillometric findings in the feet may be applied to the histamin test. Further comment upon the variations would be mere repetition.

A comparison of these two methods of study is arranged in Table 4:

TABLE 4.—COMPARATIVE FIGURES AND PERCENTAGES OF OSCILLOMETRIC READINGS AND HISTAMIN REACTIONS.

	Series A (78 cases).				Series B (72 cases).			
	Normal.		Below normal.		Normal.		Below normal.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Legs:								
Oscillometer	76	97.4	2	2.6	23	32	49	68
Histamin	77	98.7	1	1.3	19	26.4	53	73.6
Feet:								
Oscillometer	56	71.8	22	28.2	7	9.72	65	90.3
Histamin	56	71.8	22	28.2	6	8.33	65	90.3

Summarizing the merits of the histamin reaction, a prompt normal reaction is indicative of a satisfactory peripheral circulation. It may be looked upon as a guide for the condition of the capillaries and peripheral circulation and gives us information indirectly as to the status of the deeper and larger vessels. This information may be of value in determining whether there is sufficient or ample blood supply to that extremity. It may indicate the presence of an adequate circulation when dealing with pathologic extremities. This information may be of value in determining the site for amputation in selected cases.

Whether or not the histamin reaction test is superior to the oscillometer is not easily decided. The comparative figures in Table 4 seem to be slightly in favor of the histamin test. This slight advantage may be counterbalanced by the fact that the element of personal equation enters in the interpretation of the results and in the technique. Judging from Table 4, one can see that the two tests employed have practically similar percentages. When the oscillometer checks up with the clinical picture, almost invariably the histamin shows the same result. When one test does not confirm the clinical picture, as a rule the other gives a similar result. When the histamin test and the oscillometer indicate good function or a deficient circulation, experience has taught us to accept their findings regardless of the results of the Roentgen ray or the presence of some isolated symptoms or signs.

Discussion of the Significance of the Various Accepted Symptoms and Signs in Deficient Circulatory Function. An analysis of the incidence of these symptoms was made in both series. The results are arranged in Table 5:

TABLE 5.—FREQUENCY AND PERCENTAGES OF SYMPTOMS IN GROUPS A AND B.

	Series B (72 cases). (Pathologic.)		Series A (78 cases). (Efficient.)	
	Cases.	Per cent.	Cases.	Per cent.
Cramps	42	58.3	29	37.0
Coldness	42	58.3	27	34.6
Pains	43	59.7	16	20.5
Numbness	15	20.8	8	10.2
Burning	7	9.7	6	7.6

Glancing over the table, one is impressed not only with the comparatively low percentages of such prominent symptoms as cramps, coldness and pains in the pathologic group but also their unexpected frequency in the series of patients with efficient circulation.

An analysis was made of the 42 patients in the pathologic group who complained of cramps. As a rule, this symptom is accompanied by one or more of the other complaints. In 6 cases, cramps were the only complaint. Similarly, in 36 of the 42 patients there were other physical evidences of deficient blood supply.

The circulatory function tests showed an impaired circulation in 31 of the 42 patients.

In Series A, the efficient group, there were 29 patients (37 per cent) who complained of cramps. The absence of the more complete combination and array of symptoms and signs was apparent. Although coldness of the part was also present on examination in 17 of the 29 cases, the physical signs failed to point definitely to impaired circulation. The circulatory tests likewise failed to confirm any suspicions of deficient circulation in 27 out of the 29 cases. Eighteen of this group were Roentgen rayed; in 15 cases there were no evidences of calcification.

From the above analysis we may conclude that such symptoms as cramps, coldness and pains appearing in one combination or another are significant when they are confirmed by the various tests for circulatory function. While single symptoms may cast suspicion upon the efficiency of the circulation, they often fail to receive adequate support from the other methods of study. This is particularly true with such symptoms as coldness of the feet and a history of pain which may be vague and, in many instances, may be attributed to some orthopedic condition or to neuritis.

Discussion of Results and Significance of the More Prominent Signs Found in Circulatory Disturbances. In the course of the physical examination, the following findings were emphasized: (a) The degree of pulsation of the dorsalis pedis artery, whether absent, questionable, diminished or good; (b) evidence of sclerosis to the palpating finger; (c) coldness; (d) the lesions mentioned above in the introductory remarks, and (e) the condition of the veins. The relative frequency and percentage of the various signs are arranged in Table 6:

TABLE 6.—INCIDENCE AND PERCENTAGES OF THE SIGNS IN THE TWO GROUPS.

	Series A (78 cases). (Efficient circulation.)		Series B (72 cases). (Pathologic group.)	
	Cases.	Per cent.	Cases.	Per cent.
Pulse:				
Good	61	78.2	19	26.3
Questionable	6	7.6	4	5.0
Diminished	11	14.2	22	30.5
Absent	27	37.5
Sclerosis:				
Present	6	7.6	57	79.1
Suggestive	10	12.8		
Coldness: Present	22	28.2	57	79.1
Lesions:				
Present	13	16.6	52	72.2
Suggestive	7	8.9	5	6.0
Veins:				
Varicose	8	10.2	7	9.7
Thrombophlebitis	15	19.2	14	19.4

* 23 (29.5 per cent). † 49 (68 per cent). ‡ 21 (29.1 per cent).

(a) *The dorsalis pedis pulse* seems to be the main objective when one is searching for information concerning the circulation of the feet. It is easily found on the outer aspect and running parallel to the first metatarsal bone. It is superficial and can be rolled by the palpating finger, thereby giving us some information as to the presence or absence of sclerosis.

A good pulse was noticed in 61 cases (78.2 per cent) in Series A; in 6 patients the pulse was diminished, and in 11 patients the pulse was questionably diminished. One may expect to find a certain percentage of presumably normal patients with some diminution of the pulse. However, the pathologic group showed that in 19 patients (26.3 per cent) there was a good dorsalis pulse. The relatively high percentage of good pulsation in patients who have definite evidences of arterial disease is sufficient ground to question the reliability of this sign as a guide for studying the circulation. It may be of interest to mention that among the 19 patients with good dorsalis pulsation, there were 3 patients with diabetic gangrene, 3 with threatened gangrene, 1 with a trophic ulcer, and 1 patient had arteriosclerosis with claudication. Although in some cases of diabetic gangrene a good pulse may be explained by our more modern conception of the pathogenesis of gangrene along the lines of deep infection and mechanical interference of the local blood supply, nevertheless we must take cognizance of the fact that a good pulse may give us a false sense of security.

(b) *Sclerosis* of the dorsalis pedis artery was found in 57 patients (79.1 per cent) in the pathologic group, and in 6 cases (7.6 per cent) of the presumably normal group, Series A. Its presence signifies that changes have taken place in the arteries and further investigation with circulatory function tests and Roentgen ray studies are warranted. The finding of sclerosis and its value as a guide to

circulatory function is questionable. It does not necessarily prove that all the vessels are similarly involved, and the always existing question of an adequate collateral circulation having been established, must be kept in mind.

(c) *Coldness* was found in 57 cases (79.2 per cent) of the pathologic group, but was also present in 22 of the efficient circulation series (28.2 per cent). Although its high incidence in the pathologic group is similar to the frequency of sclerosis, one hesitates to attach the same importance and significance to this finding because it is more or less common and is met with in too high a percentage among the normals.

(d) *Lesions*. The variety of lesions which may be found in the lower extremities, and their significance, were discussed in detail in a previous publication. They were found either singly or in combination. The presence of these lesions indicates that pathologic changes have taken place in the smaller vessels and indirectly suggest involvement of the larger arteries. Such individuals may be labeled as potential cases of gangrene. The importance of their early recognition is obvious.

(e) *Veins*. Changes in the veins in the form of varicosities or thrombophlebitis were found in 23 cases (29.5 per cent) in Series A, and 21 cases (29.2 per cent) in the pathologic group, Series B. Although it is possible that infection in the veins may ultimately have some influence upon the condition of the arteries, as in Buerger's disease, the similar percentages in both groups fail to establish this possibility as a factor in determining the status of the circulation. However, the number of patients with varicose veins observed in these studies is too small to warrant any conclusions.

Roentgenographic studies were carried out in 111 patients; 48 in Series A and 63 in Series B. In the pathologic group (Series B), 51 cases (81 per cent) out of the 63 showed evidences of calcification; in 12 cases (19 per cent) there were no evidences of disease noted in the vessels despite the fact that the history, physical examination and the circulatory tests all indicated a deficiency of the circulation.

The records of these 12 cases were examined in an effort to learn why the Roentgen ray reports were negative when all the evidence pointed to the presence of a pathologic condition. In this group were found cases of Raynaud's disease, thromboangiitis obliterans, acute thromboarteritis, embolic occlusion and 8 diabetics, 4 of whom had threatened gangrene. In Raynaud's disease and embolic occlusion the vessels in the involved area may be perfectly normal, the seat of the trouble being higher up; the Roentgen ray therefore cannot be expected to offer us any assistance. In Buerger's disease the underlying lesion is one of inflammation, chronic and insidious in character, and the value of Roentgen ray in making the diagnosis is questionable. Samuels²³ noticed that in many cases of thromboangiitis obliterans the Roentgen ray findings are negative, unless

this condition develops in older patients who have arteriosclerosis, in which event the roentgenogram may show evidences of calcification.

In diabetics who have a tendency to develop atheromatous changes in the vessels with a resulting deficiency in circulation, it is a question whether Roentgen ray examination can detect this pathologic condition of the arteries.

The results in the efficient circulation group showed 39 cases with negative findings and 9 cases with evidences of calcification. Of the 9 cases with calcification, 8 had a good dorsalis pedis pulse and the circulatory function tests showed an efficient circulation in practically all of them.

It would seem that the attitude to assume in these cases is that the Roentgen ray gives us information as to the presence or absence of calcification, the degree of calcification, and what vessels are involved. However, it is important for one to have a clear idea that calcification of an artery is one thing and that the status of the circulation of this vessel is another. The presence of sclerosis and calcification does not necessarily mean that the circulatory function has been definitely impaired. Then again we must remember that even in extensive arteriosclerosis there may have been established an adequate collateral circulation with a satisfactory blood supply to the parts. This may explain the good results of the circulatory function tests in some cases of arteriosclerosis.

Summary. The importance of studying circulatory function in the extremities is stressed. The various methods of investigating the status of the circulation in the lower extremities have been enumerated and analyzed.

The suggestion that the ordinary methods of careful history taking and a thorough physical examination will yield sufficient and satisfactory information is questioned.

The symptoms and signs of deficient circulation were studied in 150 patients. Oscillometric readings and the reaction of the capillaries to histamin were observed in each patient. Roentgen ray examinations of the vessels were made in 111 patients of the series.

The cases were placed in two groups: Series A, including the 78 cases where the circulation was found to be efficient and presumably normal, and Series B, with 72 cases, where evidences of impaired circulation were found.

Evaluation of the individual tests proved difficult and the conclusions must necessarily be more or less arbitrary. However, one may get some comprehensive idea of what may be expected of these methods of investigation.

Conclusions. The merits and failures of the various methods of study appear to be as follows:

The *oscillometer* measures the degree of pulsation of the vessels in a particular area without personal equation as an arbitrary factor

in determining results. It gives information about the deeper vessels which cannot be palpated. It may suggest the existence of collateral circulation when definite lesions of the vessels are apparent. In some cases, hypertension may give higher readings. It compares favorably with other accepted methods of testing circulatory function.

The readings in the legs in Series A were most satisfactory (97.4 per cent of the efficient circulation group were normal). In Series B, the pathologic group, the oscillometer indicated a deficient circulation in 68 per cent of the cases, while the remaining 32 per cent had normal readings. Hypertension and an adequate collateral blood supply may account for many of the good results of the circulatory function tests in the pathologic group.

The reaction of the capillaries to histamin indicates the condition of the superficial circulation and indirectly of the deeper vessels. It may be employed as a guide to the capillary circulation and nutrition of the tissues. This information may be of practical value to the surgeon when considering the site for amputation. It is also a good guide in determining the status of the circulation. In this respect it ranks with the oscillometer in value. In the efficient circulation group, Series A, the histamin reaction in the legs showed a normal result in 77 cases out of 78 (98.7 per cent). In the pathologic group, delayed reactions were found in 73.6 per cent of the cases. The discrepancy is explained on the basis of the successful establishment of collateral circulation.

The outstanding *symptoms* such as cramps, coldness, pains, numbness and burning are analyzed relative to their frequency and significance. Cramps and coldness are mentioned as complaints in 42 cases (58.3 per cent) in Series B, but were also found in 37 and 34.6 per cent respectively in the efficient circulation group. Pain was recorded in 59.7 per cent of the pathologic group and in 16 cases (20.5 per cent) in Series A. Symptoms, particularly when two or more are present, may suggest circulatory disturbances, but these suspicions must be confirmed by the various tests for studying the circulation.

Physical examination of the extremities may throw some light upon the status of the circulation by ascertaining the dorsalis pedis pulse, palpating for sclerosis as well, noting the warmth or coldness of the foot, searching for various types of lesions and the condition of the veins. A good pulse is a welcome sign but may give misleading information as to the exact condition of the other vessels. Similarly, the presence of sclerosis need not necessarily mean that the circulation is impaired.

Roentgen ray studies in 111 patients of the 150 showed evidences of calcification in 51 cases out of 63 (81 per cent) in Series B, the pathologic group, and in 12 cases (19 per cent) the findings were

negative. In the efficient circulation group, out of 48 cases studied, 39 were negative and 9 showed calcific deposits in the vessels.

The possibility of good circulation function existing despite evidences of calcific deposits in the vessels is discussed. It is questionable whether the Roentgen ray will reveal early atheromatous changes in diabetic vessels and the inflammatory changes in Buerger's disease.

Conclusions. The usual symptoms and signs that one expects to find in patients with impaired circulation are often unreliable. When they are present in combination, circulatory disturbances may be suspected. However, in order definitely to establish the diagnosis of arterial disease, the various circulatory tests should be employed.

All of the newer methods of study have merit. Some are more practical than others and may be more readily applied. The oscilometer and the capillary response to histamin are especially valuable in determining the status of the circulation, particularly to exclude pathologic conditions, and are fairly good guides in determining the presence of an efficient collateral blood supply.

Skin surface temperature studies are of value in distinguishing the vasospastic from the occlusive form of arterial disease.

Information derived from the various tests may be helpful (1) to the surgeon when the question arises as to the advisability of operation for the relief of arterial spasm; (2) when amputation has been decided upon, in some selected cases, the site for operation may be determined by the results of the studies; (3) in differential diagnosis of vascular disease; and (4) in early diagnosis of impaired circulation.

NOTE.—The author gratefully acknowledges the many courtesies of Dr. Thomas McCrae and of the visiting physicians to the Philadelphia General Hospital and Jewish Hospital for the privilege of observing patients on their services.

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REVIEWS.

DISEASES OF THE THYROID GLAND. By CECIL A. JOLL, M.S., B.Sc. (LOND.), F.R.C.S. (ENG.); Senior Surgeon to the Royal Free Hospital and the Miller General Hospital; Surgeon to the Cancer Hospital, etc. Pp. 682; 283 illustrations and 24 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, Cloth, \$20.00.

AMONG the several monographs on this subject that have recently appeared, this one by Joll is perhaps the most comprehensive and as a reference work it probably has no equal. The preliminary chapters on the anatomy, embryology and physiology are complete in every detail. Then there are chapters on the rarer diseases of the thyroid such as acute thyroiditis, tuberculosis, syphilis, Riedel's disease, lymphadenoid and parasitic diseases. In the first part of the book are also included chapters on the parathyroids and thyroglossal cysts and tumors.

An extensive section of the book is given over to the discussion of simple goiter, which the author divides into three classes: parenchymatous, colloid and nodular. As parenchymatous goiter he considers the thyroid enlargement due to an increase in the epithelial elements of the gland without appreciable colloid accumulation. The nodular goiters are divided into those which are diffuse or multiple (adenoma) and the localized or single, in which he includes the colloid adenoma, fetal adenoma and non-parasitic cysts. These diseases are considered in detail, pointing out the symptomatology, pathology and the prophylactic as well as the active treatment.

The author gives his own classification of malignant thyroid tumors, which he treats by radical resection followed by radium or Roentgen irradiation. Thyrotoxicosis is treated more fully than any of the other diseases, and the reader is enabled to gain a picture of the disease from the time of Parry and Basedow to the present. In discussing the etiologic factors the author takes issue with Crile's theory that thyrotoxicosis is due fundamentally to disorder of the adrenals. He concludes: "It is doubtful that there is any firm basis for the theory of an adrenalin origin for exophthalmic goiter or that operations on the adrenal glands for thyrotoxicosis are justifiable." In discussing the pathogenesis of thyrotoxicosis, the neurogenic, thyrogenic, endocrine and constitutional predisposition theories are described. The symptoms and their causes are discussed in detail, giving the various technics for estimating the basal metabolic rate. There is a comprehensive chapter on the cardiovascular system in toxic goiter. Under the medical treatment, rest in bed, diet, sedatives, cardiac stimulants and iodine are discussed, as well as the dangers of the latter drug. Radiological treatment is reserved for the primary form of thyrotoxicosis associated with great restlessness and irritability and a large goiter. The surgical treatment of thyrotoxicosis is classified under three heads: intraglandular injections, ligation of thyroid arteries and thyroidectomy. The first method the author describes but does not recommend; ligation of the superior arteries however, he believes to be a useful operation. Thyroidectomy is discussed with much detail of pre-operative preparation, anesthesia and surgical technic. Complications and treatment are also fully considered.

The book is beautifully printed and illustrated, many of the anatomical and histologic plates being in color. The pen and ink illustrations of the operative technic, however, fall below the standard set by the other illustrations. Full references are given at the end of each chapter. The author's style is clear and fluent and although he mentions the work and views of other writers, he invariably expresses his own opinions based on his own wide experience.

L. F.

THE ELDRIDGE REEVES JOHNSON FOUNDATION LECTURES. *Adventures in Biophysics*. By A. V. HILL, Sc.D., LL.D., M.D., F.R.S., Foulerton Research Professor of the Royal Society. Pp. 162; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Distributor: Charles C Thomas, Springfield, Ill. Price, \$3.00. *The Mechanism of Nervous Action*. By E. D. ADRIAN, M.D., D.Sc., F.R.S., F.R.C.P., Foulerton Research Professor of the Royal Society. Pp. 103; 35 illustrations. Philadelphia: University of Pennsylvania Press, 1932. Price, \$2.00.

THE Johnson Foundation for Research in Medical Physics was established in 1929 at the University of Pennsylvania. Its purpose is to further research in the physical aspects of the medical sciences and generally to develop the relation and application of physics to medicine. As part of these activities the Johnson Foundation Lectures were begun in 1930 as a means for presenting from time to time outstanding scientific advances in such fields of investigation. The two volumes here reviewed are based upon the first two lectures. The Director of the Foundation deserves congratulations for his choice of lectures. Professors Hill and Adrian are not only scientists of international repute—both are winners of the Nobel prize—but they have the faculty of presenting in a delightful manner subjects unfamiliar to the profession at large. Yet their subjects, belonging to the relatively new field of Biophysics, are of the utmost importance to biology in general and to medicine in particular.

Professor Hill's choice of the title "Adventures in Biophysics" is a happy one. He tells in fact of his scientific adventures, of the "real reasons why we did the things we did, the delays and imperfections and perplexities which beset us, the misery of continual failure and the joy of occasional success." It is a very human account that he thus gives of his investigations of various physiologic problems of osmotic pressure of muscle and of blood, of the state of water in tissues, of the mechanics of muscular contraction, and of other subjects.

Professor Adrian's book is as readable, and as pleasantly conversational as the preceding. He tells of the development of electrophysiology, of the action of the sense organs, of pain, of discharges in motor nerve fibers, and of the activity of nerve cells.

Both of these little books are well worth the reading; they not only tell of new advances in knowledge, but are written by men who were largely responsible for making the advances; and with all, they give a vivid account of the human side of scientific research.

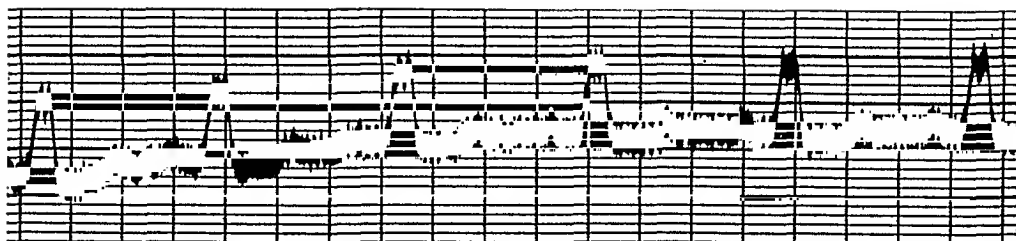
B. L.

ROBERT KOCH. I. TEIL 1843-1882. By BRUNO HEYMANN, A. O. Professor an der Universität zu Berlin. *Grosse Männer Studien zur Biologie des Genies*. Herausgegeben von Wilhelm Ostwald. Zwölfter Band. Pp. 353; illustrated. Leipzig: Akademische Verlagsgesellschaft m.b.H. 1932. Price: paper, 16 M.; cloth, 18 M.

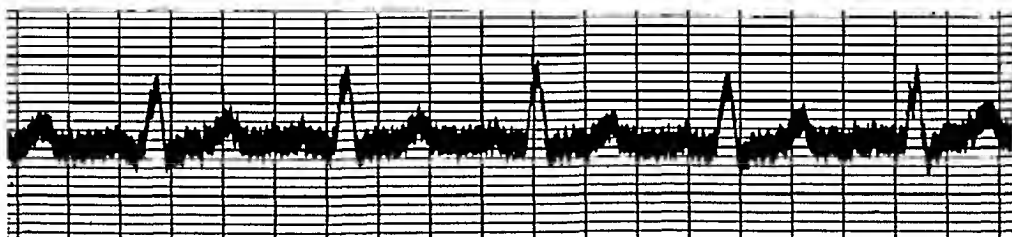
THIS, the 12th volume of Ostwald's series of biographical studies on the biology of genius, plunges *in medias res* in a way that gives but little information about the rest of the series. Without Preface or Introduction, the story begins with a description of Koch's birthplace and his ancestors which soon leads to details of his own birth and youth. And so it runs through 330 pages that, appropriately for the year 1932, carry us to the discovery of the tubercle bacillus. The etiology of anthrax, technical bacteriologic and photomicrographic procedures, etiology of wound infections and such like furnish the bulk of the subject matter. Paper, type and illustrations are excellent, and the Reviewer wishes especially to commend the different headings at the top of each page, instead of the customary endless repetition of the titles of the book and chapter.

E. K.

Lead I



Lead II



Lead III

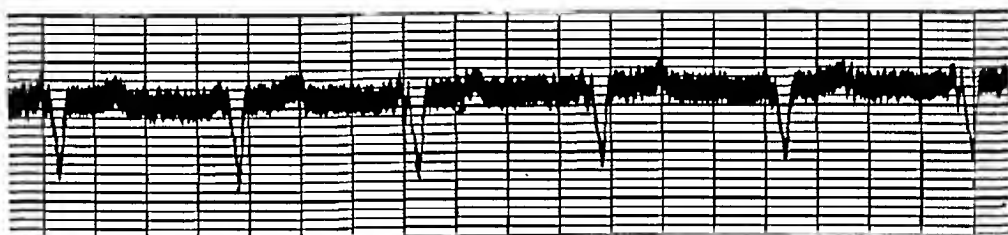
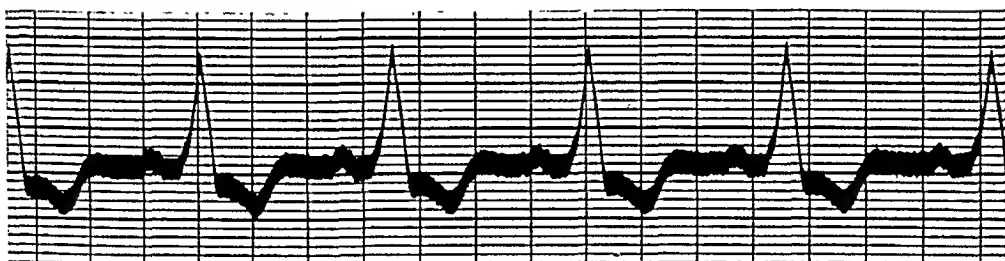
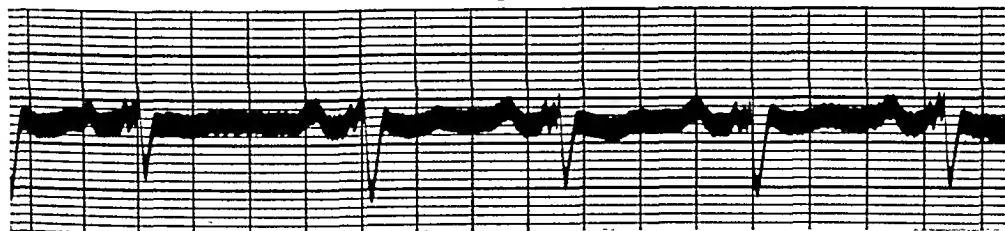


FIG. 1.—Left bundle-branch block—homophasic type.

Lead I



Lead II



Lead III

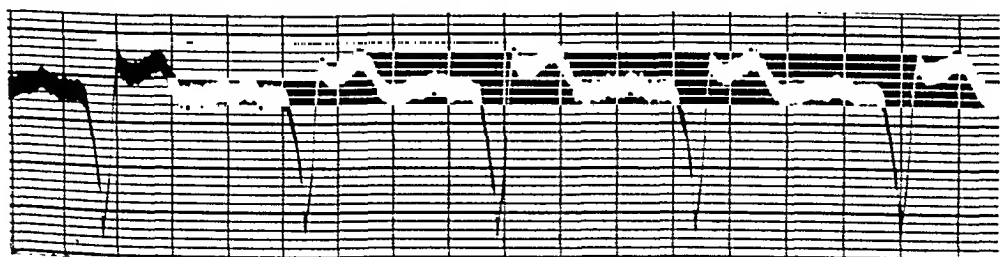


FIG. 2.—Left bundle-branch block—heterophasic type.

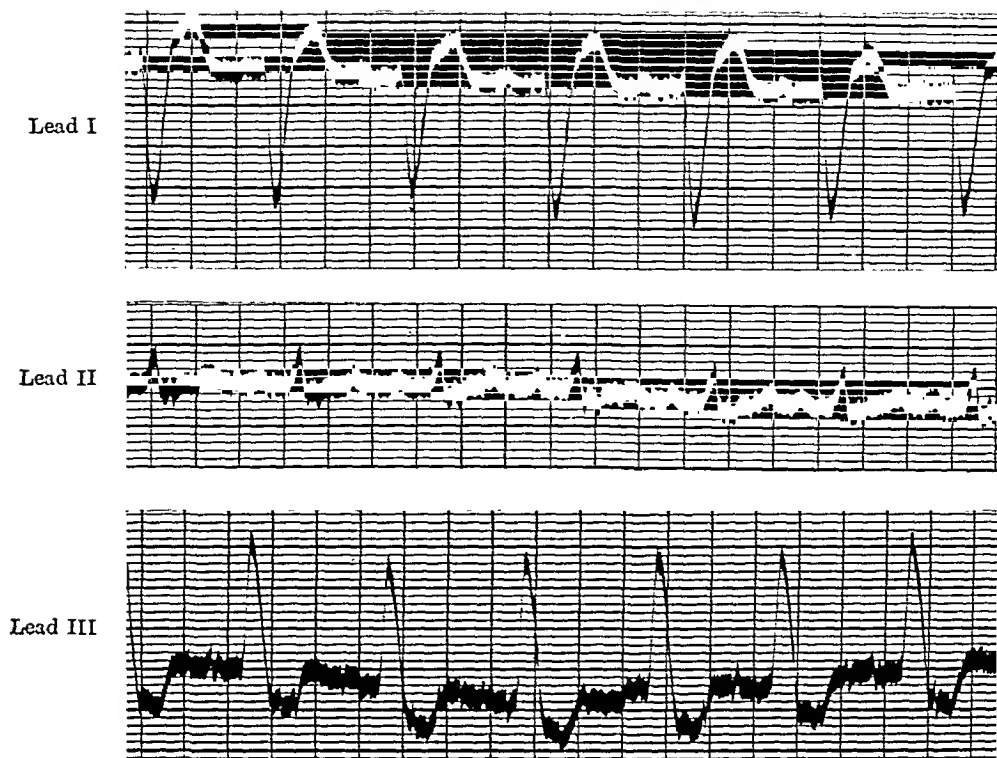


FIG. 3.—Right bundle-branch block—heterophasic type.

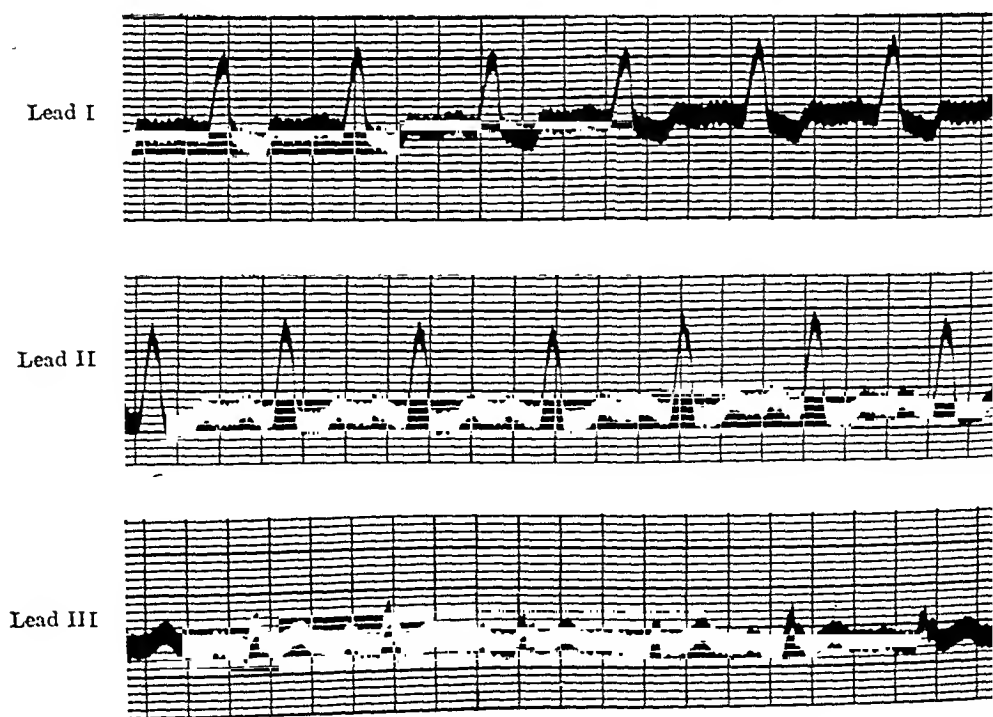


FIG. 4.—Bundle-branch block—indeterminate type.

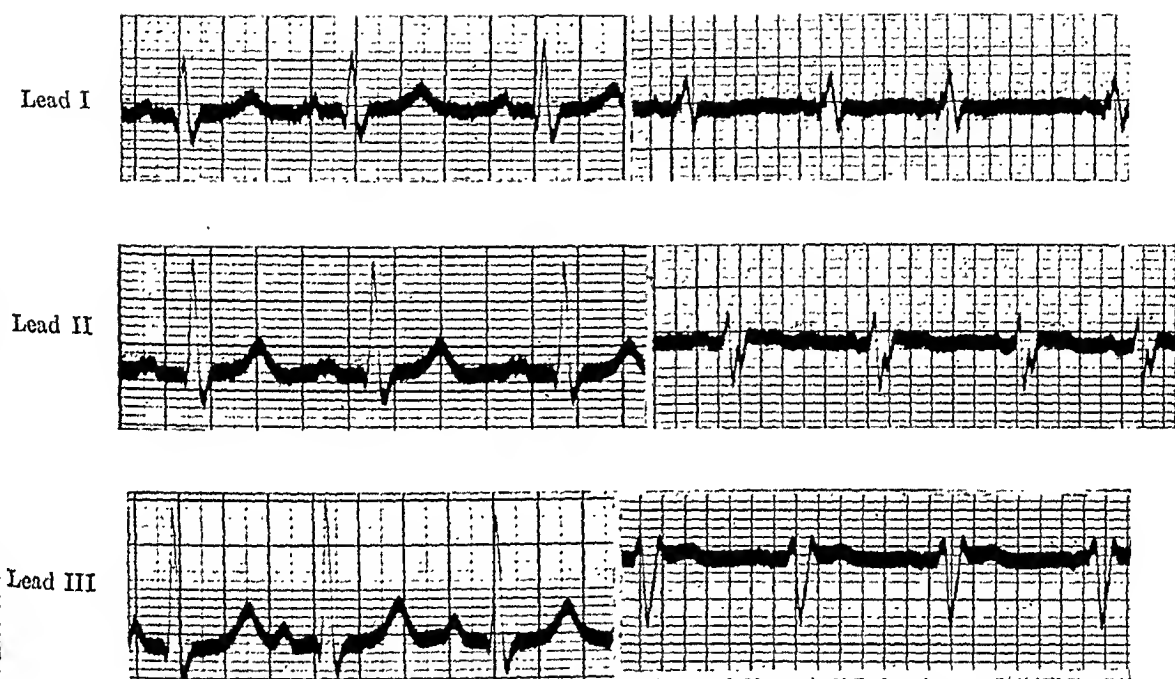


FIG. 5.—Curves showing significant aberration of the ventricular complexes.



activity than other tissues in either the infected or normal rat; that the leprous tissue is remarkably constant in lipolytic action compared with other tissues, and that the presence of severe leprous lesions lowered the lipolytic activity of most of the tissues in the body.

SURGERY

UNDER THE CHARGE OF

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Postoperative Pulmonary Complications.—Ever since the introduction of ether as an anesthetic agent, respiratory complications after anesthesia and operation have added to the morbidity and mortality of surgical procedures. For many years the more severe of these complications were known as "ether pneumonia." With the advent of each new anesthetic, claims were made that the incidence of respiratory complications would be reduced after its use. Unfortunately the claims too often proved to be untrue. Complications were often as frequent after local anesthesia as after general anesthesia.

In 1920, CUTLER and HUNT (*Arch. Surg.*, 1920, 1, 114) suggested that minor pulmonary infarction could account for a large number of the postoperative respiratory complications. Shortly after this the attention of surgeons was called to a hitherto rarely recognized lesion, which has since become known as pulmonary atelectasis (LEOPOLD, *Am. J. Med. Sci.*, 1924, 167, 421). Surely embolism could not account for this complication, and with increasing care in the examination of patients with respiratory complications after operation, the incidence of atelectasis has increased.

Within the past several months two articles have been published which reemphasize the incidence, morbidity and mortality of these troublesome complications (ELIASON and McLAUGHLIN, *Surg., Gynec. and Obst.*, 1932, 55, 716; KING, *Ibid.*, 1933, 56, 43). In the former study there were 120 cases with postoperative pulmonary complications in a series of 7326 operations, a morbidity of 1.68 per cent. Of the 120 cases 32.5 per cent died, which account for 15.5 per cent of their total operative mortality. The yearly variation of the complications was no greater than would be expected in this type of statistical data. The incidence of these complications in the earlier and later papers, except that of King, has been remarkably constant, 2.5 to 3.5 per cent (WHIPPLE, *Surg., Gynec. and Obst.*, 1917, 25, 621; ELWYN, *J. Am. Med. Assn.*, 1924, 82, 389). Bronchopneumonia was the complication in about one-third of the cases while atelectasis was the complication in less than one-sixth of the Eliason and McLaughlin series. Only 18 cases

of lobar pneumonia were encountered, while in 9 pulmonary embolism was the cause of the complication.

Similar to the findings of FEATHERSTONE (*Brit. J. Surg.*, 1925, 12, 487) and RAVDIN and KERN (*Arch. Surg.*, 1926, 13, 120) there were more postoperative pulmonary complications during the winter months when upper respiratory disease is more common in the community.

There is apparently no definite relationship between these complications and the anesthetic agent. The experience in the Hospital of the University of Pennsylvania, from which Eliason and McLaughlin collected their data from all the General Surgical Services, is that local and spinal anesthesia are associated with postoperative pulmonary complications just as frequently as are ether or nitrous oxid and oxygen. MCKITTRICK, McCLURE and SWEET (*Surg., Gynec. and Obst.*, 1931, 52, 898) have shown that with spinal anesthesia there has been an increase in the postoperative pulmonary complications when compared with ether. FOSS and KUPP (*Surg., Gynec. and Obst.*, 1930, 51, 798) had just as many pulmonary complications after spinal anesthesia as with inhalation anesthesia. Eliason and McLaughlin believe that there is a definite correlation between the incidence of the complications and the duration of the anesthetic, although this point is still debatable. It may be that the longer period of anesthesia was required for operations which are known to be more frequently associated with post-operative pulmonary complications.

In KING's (*Surg., Gynec. and Obst.*, 1933, 56, 43) series there were 7065 operations with 426 pulmonary complications, a morbidity of 6 per cent and a mortality of 22.5 per cent in those patients who developed such complications. However, of the patients that died after a respiratory complication, the complication was the contributing cause of death in only 37, an actual mortality due to the respiratory lesion of 8.2 per cent of the respiratory morbidity. Thus, while the morbidity in King's series is higher than is that found in Eliason and McLaughlin's series, the mortality of the morbidity is considerably lower. This would seem to indicate that many of King's cases were of a much milder nature than those considered in the data of Eliason and McLaughlin. If one considers only the severe cases which King reports, his figure for the morbidity would be 0.73 per cent, which is even somewhat lower than that of Eliason and McLaughlin. In King's data the respiratory complication was the cause of, or the major contributing cause of death in 0.52 per cent of the 7065 cases; while in the 7326 cases of Eliason and McLaughlin the mortality in cases with pulmonary complication in the whole series was 0.54 per cent. Both papers report a higher incidence in men than in women, but King found no seasonal variation of the complications. In both series high abdominal operations were accompanied by a higher incidence of complications than operations on any other site.

CHURCHILL and McNEILL (*Surg., Gynec. and Obst.*, 1927, 44, 483), HEAD (*Boston Med. and Surg. J.*, 1927, 197, 83) and POWERS (*Arch. Surg.*, 1928, 17, 304) have found that following upper abdominal operations the vital capacity was reduced 50 to 88 per cent of the pre-operative level, while in lower abdominal operations it was reduced 20 to 70 per cent. OVERHOLT (*Arch. Surg.*, 1930, 21, 1282) found that a disturbance of the normal subatmospheric pressure in the peritoneal

cavity, as results after the entrance of air, causes a restriction of diaphragmatic activity, and MULLER, OVERHOLT and PENDERGRASS (*Arch. Surg.*, 1929, 19, 1322), SISE, MASON and BOGAN (*Anesth. and Analg.*, 1928, 7, 187) and PATEY (*Brit. J. Surg.*, 1930, 17, 487) have shown that following an abdominal operation there is a diminished excursion of the diaphragm, which results in diminished pulmonary ventilation. The lowered vital capacity is probably also in large part due to a splinting of the abdominal musculature because of pain and the unwillingness of the patient to breath normally, together with the change in the intraperitoneal pressure, which is associated with an abdominal exploration. Certainly the last word has not been said on the perennial subject of postoperative pulmonary complications.

THERAPEUTICS

UNDER THE CHARGE OF

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The Danger of Peripheral Nerve Injuries from Intravenous Injection and Its Avoidance.—Following the careful observation of 5 instances of serious and lasting injury to the median nerve or to the lateral or medial cutaneous antebrachial nerves from intravenous injection of calcium preparations, ZUTR (*Deutsch. med. Wchnschr.*, 1932, 58, 1321) feels that, although the frequency of nerve injury is comparatively small, the effects are of sufficient importance to justify every effort for its avoidance. The author directs attention to the topographic anatomy of the veins and nerves lying in the elbow region and points out that the median vein which connects the cephalic and the basilic veins at the elbow is the only available one which is not accompanied by nerves or which does not overlie a nerve. Nerve damage can with certainty be avoided only if intravenous injections be made into this median vein. The author points out, however, that owing to anatomic variations, to subcutaneous fat and to the state of laxity of the subcutaneous tissues, it is not always possible to utilize this vein. Where such is not the case intravenous injections should always be made into the cephalic vein because in the event of perivenous escape of solution the only nerve which might be damaged is the lateral antebrachial sensory nerve. If, however, injection be made into the basilic vein, it is impossible to avoid the danger of damaging either the corresponding medial sensory nerve or the underlying median nerve or both of these nerves. The author points out the interesting fact that every instance of nerve damage from intravenous injections which has come to his personal attention was associated with the injection of a salt of calcium and he suggests, therefore, that especial care be observed where this drug is employed.

Intravenous Vaccine Therapy in Chronic Arthritis.—CLAWSON and WEATHERBY (*Ann. Int. Med.*, 1932, 5, 1447) report the results obtained by others as well as by themselves indicating, if not establishing, the close relation between chronic arthritis and streptococcal infection. They also present the results of a series of animal investigations which show that subcutaneous administration of vaccine produces relatively little increase in immunity as measured by the agglutination titer and by local tissue response to the subcutaneous injection of living streptococci. At the same time subcutaneous administration of vaccine not only fails to desensitize but actually promotes hypersensitiveness or allergy. They further establish the fact that nonspecific vaccine therapy is detrimental rather than beneficial in animals. In contrast to these findings experiments indicate that the intravenous administration of streptococcus vaccine produces a very high degree of immunity combined with an effective desensitization. It is also demonstrated that the immunity is species specific for streptococci but not type specific. On the basis of these experimental results the authors treated a group of 300 patients suffering from chronic infective arthritis by weekly intravenous injections of streptococcus vaccine made from a culture obtained from a case of acute rheumatic fever and which was of low virulence because of its continued growth for 9 years. The initial dose employed was 100,000,000 organisms which was increased by 100,000,000 at each subsequent injection. Only slight reactions occurred and in only about half of the patients. The reaction seemed to be unrelated to clinical improvement. It was rarely necessary to administer more than 8 to 10 injections. Definite clinical improvement occurred in 74 per cent of the patients, questionable improvement in 6 per cent and no improvement was observed in about 16 per cent. The authors feel that this method is based upon sound experimental investigation and that the clinical results are sufficiently good to justify further employment of the method for treatment in man.

PEDIATRICS

UNDER THE CHARGE OF

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The Treatment of Coughs With Suprarenal; Whooping Cough.—BARBOUR (*Arch. Pediat.*, 1932, 49, 816) says that the many remedies which have been offered for the treatment of pertussis differ in name more than in action. None of them has produced any decline in the incidence, morbidity and mortality of the disease. Each of these remedies may be roughly classified in one of the following categories: sedatives, antispasmodics or nonspecific proteins. The effect of the sedatives and antispasmodics is probably mainly one of symptomatic relief. Although the pertussis vaccines may have some specific anti-toxin effect, the results may be attributed largely to nonspecific protein reactions. There is no consistent dependence on any one, or any com-

bination of the various remedies to give a prompt and a continued relief. Over a period of 18 months suprarenal, or thyroid and suprarenal and a nonspecific protein was administered to 85 cases. The results of the treatment were as follows: In 50 per cent (44 cases) there was a striking improvement of the symptoms within 1 to 2 days and a complete disappearance of the cough within from 1 to 4 weeks following the use of the suprarenal. In 20 per cent (14 cases) a prompt and increasing relief followed the administration of the thyroid and suprarenal. A complete cure followed within from 1 to 4 weeks. The condition of 25 per cent (23 cases) responded very well to the combined endocrine and protein treatment, with a complete disappearance of the cough in from 2 to 4 weeks. In 4 cases (5 per cent) the treatment seemed to have little or no effect. In none of the cases was there any complications or sequelæ.

Immunization Against Measles by Placental Blood.—DE SOUZA (*Arch. de méd. d. enfants*, 1932, 35, 633) during a period of 4 years injected 160 children who had been exposed to measles, with blood taken from the human placenta. The number of cases in which immunization was obtained varied between 85 per cent in the first year of the observation and 63.4 per cent in the fourth year. In those cases in which immunization failed, the measles almost always occurred in an attenuated form, generally without catarrh of mucous membranes and of the bronchi. The death rate among the patients who contracted measles in spite of the injection was only 2.27 per cent, as compared to 12.7 per cent among the noninjected patients. It is suggested that the drop in the percentage of immunizations in the fourth year was due to tyndallization of the placental blood with formaldehyde solution. This procedure was resorted to in the fourth year because of the persistence of occasional suppurations, but a much smaller percentage of immunizations were obtained with 10 cc. injections of blood so treated than with the 4 cc. injections of nontyndallized blood or of blood tyndallized without formaldehyde solution, which were given in the first 3 years. After the blood has been collected from the placenta under strict aseptic conditions and has been sealed immediately in sterile ampules, it is necessary only to tyndallize without formaldehyde solution once or twice at from 52° to 54° C. to be ready for use. The injection is usually followed by a rise of temperature which usually lasts for 2 days. The injection should be given intramuscularly and care should be taken to avoid leakage into the subcutaneous tissue. The author believes that the immunity to measles produced by placental blood is due to the individuality of this blood. With its amino acids and other hypothetic products of internal secretion, it probably acts as a nonspecific antigen, stimulating the production of antibodies and resulting in a group immunization to anaphylactic and antiphylactoid states.

Cyanosis in the Newborn.—HUNT (*Am. J. Dis. Child.*, 1932, 44, 1268) analyzed the results obtained in 118 postmortem examinations in an attempt to determine the more common pathologic lesions causing cyanosis in the newborn. It is realized that the causes of death and of cyanosis are not synonymous, and that several facts may be involved. Hemorrhage, whether intracranial, pulmonary or intraabdominal, can-

not be disregarded as a contributing cause in many instances. Intracranial lesions, although frequently found at postmortem examinations, are not always of sufficient severity to produce symptoms. This is true especially of small tentorial tears, which must be disregarded usually. On the other hand, extensive unilateral or bilateral tears of the tentorium accompanied, as they most frequently are, by profuse hemorrhage, would seem sufficient cause for cyanosis. Meningeal bleeding may occur in the absence of tentorial lesions, and is often profusely distributed over the cerebral hemispheres or at the base. These two types of lesions are usually the direct result of birth trauma, and consequently cyanosis will appear in the first few days of life. The cyanosis accompanying congenital heart disease is due to the mixture of venous with arterial blood or to stasis. With such abnormalities, the blueness varies directly with the activity of the infant, and does not appear until several weeks after birth. Unless the lesion is severe, life is possible, and in some cases the child survives for some years. The relatively few cases that were studied in this series are not indicative of the true frequency of cyanosis as a manifestation of congenital cardiac abnormalities. Pneumonia is the most common single lesion found in these infants. The disease does not differ from that seen in older children, except for the variability of the signs. The appearance of a hyalin membrane, which is probably the result of aspirated amniotic fluid, is more common than was believed formerly. In small amounts, this is of little significance. In the cases in which it forms a membrane lining the alveoli of large sections of the lung, it cannot but cause respiratory embarrassment. Persistent cyanosis appears early in the life of these infants, and this may be the only sign present. Other pathologic conditions may produce cyanosis in the newborn, but they are relatively infrequent. The greatest difficulty in diagnosis is usually between pulmonary and cerebral lesions. Lumbar puncture or roentgenologic examination of the chest may be of assistance in establishing the cause of cyanosis, but at times these procedures may give no aid. In the infants coming to postmortem examination, intracranial lesions, including hemorrhage and tentorial tears are the most frequent causes of cyanosis, but as a single severe entity pneumonia is the prominent factor.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Vaginal Wounds Due to Intercourse.—The German literature frequently contains reports of serious vaginal wounds as the result of sexual relations, and in reporting a case of this kind SZTENLO (*Zentralbl.*

F. Gynec., 1932, 56, 2121) states that the etiology is not always the same, since in some cases it is dependent on abnormal positions during intercourse, such as knee-elbow position, unusual size of the penis and developmental anomalies of the female genital organs. The case he reports is that of a poorly developed girl, aged 20 years, who presented a tear in the right vaginal vault large enough to admit three fingers. This injury followed a normal intercourse and the hemorrhage was so severe that the hemoglobin dropped to 40 per cent. The laceration extended about 1 inch into the parametrium. The spurting bloodvessels were ligated and the wound was sutured with considerable difficulty as the sutures tended to tear out. Following suture the vagina was packed for 24 hours. It is interesting that the large majority of such vaginal injuries occur on the right side, as in this case, and he believes that this selection is due to some anatomic reason. Since the rupture in this case followed intercourse in the normal position it was probably due to hypoplasia of the vaginal wall, especially since the vagina was so friable when suture was attempted and the girl was generally poorly developed. In a collected series of Neugebauer there were 22 deaths among 157 cases, the mortality being due to hemorrhage, sepsis and peritonitis. The treatment of such injuries consists primarily of arresting hemorrhage. If the wound is recent and uncontaminated, suture of the edges suffices, but in wounds of longer duration, after controlling hemorrhage, drainage should be instituted for a few days.

Uterine Allergy.—In stating that uterine symptoms may be due to food allergy, ROWE (*Am. J. Obst. and Gynec.*, 1932, 24, 333) has given the gynecologists something to think about. The abundance of smooth muscle and of mucous membrane in the tubes, uterus and vagina emphasizes the probability that allergic reactions may occur in this tract even as they do in the bronchial or gastrointestinal tracts. He believes that painful, irregular, scanty or profuse menstruation may be due to food allergy. Such disturbances may be associated with severe nausea, vomiting, acidosis, migraine, headaches or other allergic disturbances. Careful study of the patient with physical and laboratory examinations must be made so that all existing pathology is discovered. Gynecologic lesions of all types must be ruled out in patients suspected of allergy, but it should be remembered that allergic reactions may accompany other disease pictures. Skin tests with all foods and preferably with other types of allergens should be carried out. Elimination diets modified by skin reactions to foods, as well as by a history of specific food idiosyncrasies, should be prescribed. By the gradual development of such diets the allergy-producing foods can be discovered. Other conditions aside from abnormal uterine bleeding, which he believes may sometimes be of allergic nature, include leukorrhea, edema of the tubes, vagina or labia and excoriation of the labia and of the surrounding skin.

Menorrhagia Due to Blood Dyscrasias.—The occurrence of menorrhagia is so frequently due to some lesion of the female generative organs that blood dyscrasias are not often considered as causative factors. KAHN (*J. Am. Med. Assn.*, 1932, 99, 1563) studied 45 cases of blood disease in women during the reproductive period, and found that a normal menstrual flow was present in 51 per cent, there was

excessive flow in 33 per cent, while in 15 per cent it was diminished. The menstrual deviation figured prominently in the symptom complexes which brought these patients to their physicians. He believes that sufficient emphasis has not been placed on disturbance of the menstrual flow occurring in those cases in which no pelvic abnormality is present. In some cases curettage has been performed, but the bleeding soon recurs. In such cases a complete study of the blood will sometimes reveal an underlying blood disease as the etiologic factor, the menstrual disturbance being but a local manifestation of a systemic disorder.

OPHTHALMOLOGY

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Eclampsia With Amaurosis Due to Detachment of the Retinae.—CROWTHER and HAMILTON (*Med. J. Australia*, 1932, 2, 177) report bilateral detachment of the retina occurring in a primipara, aged 23 years, who developed eclampsia in the seventh month of pregnancy. On the date of her admission to the hospital, marked generalized edema was present, the systolic blood pressure was 200 and the urine contained large amounts of albumin. Blurring of vision commenced the next day and progressively increased to almost total amaurosis in 8 days. The patient was delivered on the seventh day and had an eclamptic convulsion shortly afterward. Her condition improved rapidly after delivery. She left the hospital in 3 weeks and showed no evidences of residual chronic nephritis. Marked generalized edema of the retina with detachment of the lower and temporal portions was present in each eye when the patient was first examined 1 day after delivery. Reattachment of the retina was complete in 3 weeks. Residual pigment changes were striking. Vision had improved in 1 month to 6/36 right and 6/24 left, with proper refractive correction. Hamilton thinks that the edema of the retina was a part of the generalized edema of the body tissues. The dark color of the detachment in its acute stage and the residual pigment changes suggest that the source of origin of the edema was the choriocapillaris, so that the detachment involved both the retina proper and the retinal pigment epithelium.

Association of Sclerosis of the Cerebral Basal Vessels With Optic Atrophy and Cupping.—KNAPP (*Arch. Ophth.*, 1932, 8, 637) reports 10 cases of optic atrophy with excavation of the disks simulating that of glaucoma, but without elevation of the intraocular tension. Such cases have usually been considered as atypical glaucoma, the optic atrophy and excavation having been caused by a previous rise of tension,

by inherent weakness of the lamina cribrosa, or by a solution of the nerve fibers by an abnormal action of the intraocular fluid as it passes through the optic nerve. The field changes in these 10 cases were different from those usually seen in glaucoma. There was a tendency to altitudinal defects and the blind spot changes were not characteristic. The progress of the loss of vision was very slow. An operation for the reduction of tension was performed in 2 of the cases without any effect on the course of the disease. The patients in this series showed general symptoms of a moderate general arteriosclerosis without particular cerebral manifestations. Their ages varied from 53 to 75 years. Stereoscopic roentgenograms of the head revealed in all cases calcification of the internal carotid, posterior communicating, or ophthalmic arteries. The author believes, therefore, that the optic atrophy in these cases is of descending type, due either to direct pressure of sclerosed basal vessels on the optic nerves anterior to the chiasm, or to the development of areas of softening in the nerves from closure of nutrient bloodvessels.

The Prognosis of Albuminuric (Angiospastic) Retinitis.—HEIDER and LÜRMANN (*Münch. med. Wchnschr.*, 1932, 79, 1585) believe that the retinitis which occurs in chronic nephritis and that in malignant nephrosclerosis (malignant hypertension) are of the same type and have the same ophthalmoscopic appearances and the same pathogenesis (angiospasm). In general they have also the same serious prognosis. Healing or improvement of the retinitis and improvement of the systemic condition occur in a certain number of cases, especially in acute nephritis and eclampsia. In chronic nephritis and in malignant nephrosclerosis, as a rule, any resorption of the retinitis is only temporary and fresh lesions recur until the time of death. The occurrence of angiospastic retinitis in primary hypertension without renal insufficiency indicates the approach of renal failure which may, however, be postponed for several years. The occurrence of arteriosclerotic retinitis does not have the same significance. In patients with malignant nephrosclerosis with manifest renal insufficiency and retinitis the outlook is uniformly hopeless. The development of angiospastic retinitis is a similarly ominous sign in chronic nephritis. However, an edematous retinitis which develops coincident with a state of pseudouremia in a chronic nephritis in the stage of renal insufficiency, or in a malignant nephrosclerosis, will subside rapidly under proper management of the systemic condition, and the patient may live comfortably for several years without recurrence of the retinitis. The authors believe that both the cerebral manifestations of the pseudouremia and the retinitis are due to edema consequent upon arterial ischemia of the brain and retina. With the relief of the arterial constriction the edema subsides, the cerebral manifestations and the retinitis disappear, and the patient returns to his former status. This improvement is usually associated with a drop in blood pressure. If retinitis develops in malignant nephrosclerosis without associated pseudouremia, though temporary regression of the retinitis may occur either through a lowering of the blood pressure or through improvement in the strength of the heart, there will be no permanent alteration of the patient's condition or of the ultimate prognosis.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Relation of the Histopathology of Nasopharyngeal Neoplasms to Their Radiosensitivity.—To Kocher, once said Pirogoff, "The most perfect satisfaction which one can have in medicine comes through the thorough study of one special chapter in every direction and from every point of view. . . ." And so, beginning with the clinical observation that some pharyngeal neoplasms responded much more readily to radium therapy than others, the oncologist—by subjecting his problem to virtually every available form of investigation—not only has told us why, but also has shown us how fruitfully to apply this knowledge to human needs. Not untimely, therefore, BECK and GUTTMAN (*Ann. Otol., Rhinol. and Laryngol.*, 1932, 41, 349) recount the circumstances which have led up to the recognition of the three commonly encountered neoplasms arising from epithelial structures of the oropharynx and nasopharynx. Histopathologically, these three malignant tumors are called: (1) Squamous-cell carcinoma; (2) transitional-cell carcinoma, and (3) lymphepithelioma. Each of these neoplasms presents an individually characteristic microscopic picture. Clinically, too, the transitional-cell carcinoma and the lymphepithelioma behave similarly—in that, though small (often grossly undetectable), they metastasize early to cervical lymph nodes, and their anaplastic cells are precociously sensitive to radium. Contrariwise, the squamous-cell carcinoma usually can be found without difficulty, grows slowly, invades regional lymphatics relatively late, and the well differentiated cells are notoriously "radio-resistant." It follows, then, that at the present time surgery offers most for the well-known squamous-cell types, and radium for the other two; that here, as always, efficient treatment depends upon correct diagnosis; but that if, for any reason, the histopathologic diagnosis is unavoidable or doubtful, the imperativeness of prompt action justifies the employment of a "therapeutic test"—which in this case is radium.

Ten Commandments for Sinus Sufferers.—The more expediently to manage their cases, MANDELBAUM (*Laryngoscope*, 1932, 42, 710) issues to his patients with paranasal sinusitis certain data designed to facilitate recovery and to prevent recurrences. Briefly, these admonitions, or "commandments," may be set forth as follows:

1. Do not wet your hair on leaving your home in the morning, particularly in cold weather.
2. Do not swim or dive.
3. Do not get wet feet.
4. Do not smoke or "drink" during acute attacks.
5. Do not go without a hat except in the midsummer months, and not even then too long in the very hot sun.

6. Do not stay in a draught either while asleep or awake.
7. Do not overindulge in food.
8. Do not take cold shower baths in the morning, particularly in cold weather, unless donning a rubber cap. If you must do so, do not leave the house before your body is warm. Better still, bathe before retiring.
9. Do not wear summer underwear in the late fall, winter or early spring.
10. Do not neglect your general health.

RADIOLOGY

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A Critique of the Roentgen Signs of Infantile Scurvy.—After enumerating the accepted roentgenologic signs of infantile scurvy KATO (*Radiology*, 1932, 18, 1096) holds that there is but one conclusion to draw, namely, that the majority of these signs are not pathognomonic. The continued use of such terms as the "Trummerfeldzone" and "Wimberger's sign" as diagnostic of infantile scurvy leads to confusion. Pelkan's triad in the diagnosis of latent scurvy is a valuable adjunct, but it is not absolutely characteristic. Beading of the ribs is common both in infantile scurvy and rickets. Separation of epiphyses is found most frequently in infantile scurvy, but it may also occur in other conditions. The white line of Fraenkel is the least characteristic of scurvy for it is merely a phenomenon of hyperealcification at the end of a long bone, which is seen in many diverse pathologic conditions. The one sign which is absolutely unique in infantile scurvy is that of subperiosteal hemorrhage during the third stage of the disease. This can only be inferred clinically, and the final diagnosis must rest on the roentgenologic evidence. The author insists that these criticisms do not constitute an attempt to minimize the diagnostic value of the Roentgen evidence, but he desires to emphasize the necessity of broadening the experience of both clinicians and roentgenologists in evaluating and interpreting the roentgenologic signs of infantile scurvy.

Evaluation of Pneumoventriculography and Encephalography.—ADSON (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 657) presents a critical tabulated review of 217 cases of tumor or suspected tumor of the brain of which 187 were operated on or explored. Careful neurologic examination, with the aid of ordinary roentgenograms and ophthalmologic examination permitted localization of 69 per cent of the tumors. Ventriculography gave positive localizing evidence in 25 per cent of the cases not localized clinically. Ventriculography is of par-

ticular value when the patient is comatose and when, therefore, it is difficult to elicit neurologic signs. It is valuable in distinguishing between tumors of the frontal lobe and of the cerebellum and in the localization of basoarachnoiditis obstructing the 4th ventricle. Occasionally it may be resorted to in cases of chronic brain abscess, but it would be unwise to employ it as a routine. Encephalography is of greatest value in the differential diagnosis and localization of arachnoiditis, posttraumatic lesions and atrophy of the brain. It is an unsafe procedure in the presence of increased intracranial pressure. The author is of the impression that encephalography is being abused since the clinical features are often sufficient to make possible the diagnosis without subjecting the patient to the distressing symptoms which attend encephalography.

Spectrophotometric Analysis of the Color of the Skin Following Irradiation by Roentgen Rays.—From their investigations, HARRIS, LEDDY and SHEARD (*Radiology*, 1932, 19, 293) conclude that spectrophotometry offers an accurate method of recording changes in color of the skin following irradiation. The course of the erythema is cyclic over a period of months with fairly definite points at which the erythema is at a minimum. The pigment is immediately affected by irradiation and follows a course independent of that of the erythema; so that the hue of the skin remains constant.

Treatment of Giant-cell Bone Tumors by Roentgen Irradiation.—During a period 25 years 26 cases of giant-cell bone tumor were treated by PFAHLER and PARRY (*Am. J. Roent. and Rad. Therap.*, 1932, 28, 167). The first case is believed to be the earliest case on record and was originally considered to be osteosarcoma. All cases have shown a definite and satisfactory response to Roentgen therapy, more satisfactory in the young than in the old. The authors favor fractional doses with rays of high voltage. The damage to epiphyses was observed. They believe that irradiation is definitely superior to surgery in treating these tumors, and they hold that curetting or crushing the bone is not of advantage.

Roentgen Ray Therapy in Dermatology.—It is held by Fox (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 550) that roentgenotherapy is used too frequently and in too large doses, especially to the exclusion of other therapeutic measures, for skin diseases. A large number of superficial inflammatory dermatoses can be cured without Roentgen rays, and a still larger number can be cured with only small amounts of radiation. In fact, Roentgen rays alone produce permanent cures in a relatively small number of skin diseases. Employment of the Roentgen rays is indicated primarily in localized or infiltrating dermatoses. A generalized or universal dermatosis is by itself a contraindication for the use of Roentgen rays except for very small doses judiciously administered.

Visceral Displacement in Pneumonia.—Among 40 consecutive cases of lobar pneumonia observed by C. WU (*Radiology*, 1932, 19, 215) 5 showed displacement of the heart and trachea toward the affected side, and 22 showed elevation of the diaphragm on the affected side. Both dis-

placements were noted only on full inspiration. Displacement begins early, sometimes before it is possible to demonstrate consolidation, persists usually throughout the course of the disease, and may continue for a time after resolution has occurred. Mediastinal displacement occurs more often in children; elevation of the diaphragm more often in adults. Roentgenologic demonstration of either displacement may be important in distinguishing pneumonia from pleural effusion or other disease.

NEUROLOGY AND PSYCHIATRY

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Nonspecific Therapy in Mental Disorders.—GRAVES (*Lancet*, 1932, 9, 57), in 1922, suggested that in mental disorders injections of colloidal calcium oleate caused or increased a reaction in or around septic foci with a resulting reduction of general toxemia and improvement of nutrition, circulation and mental state. Other agents which have been widely used here are colloidal sulphur in oily or watery suspension and TAB vaccine. The focal effects of an infection consist of an active stage, appearing within 24 hours as an area of increased vascularity, pain, swelling, exudation and disturbance of function in or around any localized lesion, and a stage of resolution during which there is a progressive decrease in the inflammatory reaction until the *status quo ante* is reached or passed. If the sepsis is open the focal reaction may be enough to cause a discharge or a reduction of the persistent infection with the consequent cessation of mitigation of the toxemia and mental recovery. When the sepsis is closed, however, nonspecific therapy is not likely to bring about recovery especially if the focus contains necrotic material. The result is more likely to be increased toxic absorption, greater toxemia and exacerbation of symptoms.

Viewpoints on Stuttering.—BROWN (*Am. J. Orthopsych.*, 1932, 2, 1) gives a brief symposium on the theories and practices which are widely employed in attempting to understand, to treat and to prevent stuttering. On the basis of certain facts and principles which are common to most of these theories and practices, an attempt is made to formulate a reasonable hypothesis upon which both therapeutic and prophylactic work may be based. The following procedures are suggested as the basis of a rational method of attempting to solve the problem of stuttering which, to be more exact, is the personality problem of the stutterer: (1) The study of each stutterer as an individual personality, striving and failing to adjust himself adequately to social situations through

speech. (2) The application of accepted principles of physical and mental hygiene for the purpose of integrating the stutterer's personality and enabling him to make adequate adjustments to social situations. (3) The instruction of teachers, parents and others in the nature of these principles and the training of these persons in applying them, not only as a means of treatment but as a means of preventing stuttering. (4) The conducting of research into the cause, origin and nature of stuttering for the purpose of developing, if possible, more adequate therapeutic and prophylactic techniques.

Psychosis: Its Importance as a Presenting Symptom of Brain Tumor.

—ADELSTEIN and CARTER (*Am. J. Psychiat.*, 1932, 12, 317) state that the incidence of brain tumor as a clinical entity is about 1 per cent. The psychosis may be the first presenting symptom. They feel that all cases presenting a psychosis should receive a thorough neurologic examination to rule out a possible organic basis. Visual and auditory hallucinations are of localizing value only if distinct and apart from the psychosis. The mental phenomena in brain tumor may be regarded as focal in nature only if the neurologic examination will bear out the localization. The cases studied, the authors feel, bear out the contention of Gordon Holmes that "lesions of the frontal lobe produce mental symptoms perhaps more frequently than those of any other part of the brain except the corpus callosum."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Bacteriophage Therapy.—It is often difficult to evaluate methods of treatment in man because of the many uncontrollable factors involved. The use of animals which are subject to certain infections offers better opportunities for obtaining more reliable results. The early optimism as to the therapeutic value of bacteriophage has been succeeded by a feeling of uncertainty. COLVIN (*J. Infect. Dis.*, 1932, 51, 17) reports from the Department of Immunology, Yale University School of Medicine, that with streptococcus lymphadenitis of guinea-pigs he was unable to find any curative value in a bacteriophage which showed maximum virulence *in vitro* against the etiologic organism. He believed that within the tissues the conditions are such as to inhibit the action of a bacteriophage that is thoroughly effective *in vitro*, and from a review of the results of bacteriophage therapy in natural and experimental diseases of laboratory animals it appeared to him that there had been no real therapeutic successes since the early experiments of d'Herdelle with fowl typhoid.

Lymph Pressures in Sterile Inflammation.—FIELD, DRINKER and WHITE (*J. Exp. Med.*, 1932, 56, 363) report observations on lymph pressure in the leg lymphatic of dogs. Sterile inflammation was produced by immersing foot in hot water. A column of lymph was established by cannulating one or both of the two main lymphatics at the ankle of the hind leg and attaching to a vertical manometer through a Y tube. In one series of experiments, the foot was placed in water at 100° C. for 2 minutes. An advanced degree of inflammation resulted, with the production of lymph pressures ranging from 78 to 120 cm. of lymph. This pressure, closely following the venous pressure, rose immediately upon immersion, reaching a maximum in 3 to 4 hours. The venous pressure reaches its greatest height in about 15 minutes. Similar results were obtained in inflammation produced by exposure to temperatures of 50° to 60° C. over longer periods of time. A rise in protein content of lymph was noted. According to the authors, lymph pressure cannot be measured in a normal leg.

Studies on Gonococcus.—The failure to obtain growth on plain agar is commonly used as a criterion of the Gonococcus. SEGAWA (*Centralbl. f. Bakt.*, 1932, 124, 261), however, has shown that Gonococcus adapts itself and grows readily and in series on this simple medium when it has been transferred at least ten times on blood agar after isolation. He further found that this organism lived very much longer on plain agar either in a moist chamber or in the ordinary incubator than on blood agar. He emphasized the advantage of using such cultures for immunizing rabbits and in preparing vaccines because of the absence of the blood proteins and, using suspensions from agar cultures, he was unable to detect any varieties among thirty-five strains of gonococci which he studied by agglutination methods (p. 266) nor could he find any relationship between gonococci and any of ten differentiated meningococcus strains (p. 268). There is the possibility in the Reviewer's opinion that gonococci so adapted to grow on such an unnatural medium as plain agar may have lost in type specificity even if types of gonococci do exist which is at present unsettled.

Experimentally Induced Varieties of Pneumococci.—In the present-day state of confusion regarding the limitations in the transformation of bacterial types and of readiness to accept hypotheses based on the results obtained by experimental methods *in vitro* and in animals and applying these directly to epidemiologic and pathogenic studies in man, it is well to realize the difficulties in obtaining reliable facts. KLUMPEN (*Centralbl. f. Bakt.*, 1932, 124, 241) has systematically studied the pneumococci and the methods used for inducing variations. The addition of antiserum or small pieces of the organs of animals heated to 56° C. for 1 hour to broth cultures were the two procedures which gave uniform results. The use of optochin, yeast and optochin, bile, the picking of daughter colonies or other methods were not regular nor reliable. He improved the antiserum technique by making 4- to 6-day instead of daily transfers. Mere colony appearances of which he described a number of forms were not found to be reliable. The changes he observed never went beyond the R (rough) form, were induced by measurable injury, and consisted in loss of type specific characters, virulence and

the facility to produce capsules, but the characteristics of true pneumococci such as morphology, bile sensitivity, behavior in litmus milk, etc., were retained so that they could not be confused with such organisms as the mouth streptococci. He could not support the view that pneumococci change during convalescence from pneumococcal infections into the R form in that he was unable to demonstrate in material from healthy, sick and convalescent persons any organisms which behaved biologically like the experimentally induced R forms of true pneumococci. The virulence he believed was probably of more importance in human epidemiology and pathogenicity than the type of pneumococcus, although Types I, II and III are generally of higher virulence than the group X organisms.

HYGIENE AND PUBLIC HEALTH

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Comparison of Trachoma Virulence in Different Sections of the United States.—RICE, SMITH and SORY (*Pub. Health Rep.*, 1932, 47, 1149) note that the virulence of trachoma never has received the attention it deserves, usually the percentage of the infected in a population being stated without reference to damage done. Severity is not to be measured by deaths but by the amount of blindness and number of entropions. On this basis the disease was found to be as follows:

	No. of cases.	No. of entropions to each 100 cases of trachoma.	No. of blind eyes to each 100 cases of trachoma.
Missouri	1609	43.4	8.2
Arkansas	1037	29.7	7.4
Kentucky	5846	10.8	5.8
Tennessee	1825	6.1	1.2
South Georgia	708	1.1	0.28

Hardening Procedures and Upper Respiratory Disease (Common Cold).—GAFAFER (*Am. J. Hyg.*, 1932, 16, 233) observed over 300 adults for 35 weeks from September 29, 1929, to May 31, 1930, when every effort was made to secure reports of all attacks of upper respiratory disease (common cold). The group that during the winter slept with windows partially open, and the group that slept with windows wide open showed no significant difference in respect of (a) frequency and (b) severity of attack of upper respiratory disease (common cold). In respect of type of attack it was found that of the two groups the second (wide open windows) suffered relatively (a) fewer attacks with coryza and sore throat, and no cough; (b) more attacks with coryza, cough

and sore throat, and (c) more attacks with cough. The group that exercised outdoors less than 8 hours per week in the summer, and the group that exercised 8 or more hours per week, showed no significant difference in respect of (a) frequency, (b) severity, and (c) type of attack of upper respiratory disease (common cold). The group that exercised outdoors less than 4 hours per week in the winter, and the group that exercised 4 or more hours per week, showed no significant difference in respect of (a) frequency, (b) severity, and (c) type of attack of upper respiratory disease (common cold).

Relation Between Size of Frontal Nasal Sinuses and (1) Attacks of Upper Respiratory Disease (Common Cold) and (2) Certain Nose and Throat Conditions.—PALMER (*Am. J. Hyg.*, 1932, 16, 224) found no evidence of association between size of frontal sinus and (a) number of attacks of upper respiratory disease (common cold), (b) duration of upper respiratory attacks (common cold), and (c) the presence or absence of any one of twelve recorded conditions of the upper respiratory passages.

Endemic Typhus Fever of the United States.—DYER *et al.* (*J. Infect. Dis.*, 1932, 51, 137) state that the rat flea (*Xenopsylla cheopis*) as a vector of endemic typhus meets the requirements of the epidemiologic evidence. The virus of endemic typhus has been recovered repeatedly from rat fleas taken at typhus foci, and finally experimental transmission of the virus from rat to rat by means of rat fleas has been carried out in the laboratory. The foregoing evidence points to the rat flea (*Xenopsylla cheopis*) as a common vector of endemic typhus from rat to rat and from rat to man. The possibility must be borne in mind that rodents may be an important reservoir of typhus in parts of the world where epidemics of typhus occur, and it seems a reasonable hypothesis that epidemics of louse-borne typhus may have their origin from typhus transmitted from rat to man by rat fleas.

Is the "Appalling Increase" in Heart Disease Real?—BOLDUAN and BOLDUAN (*J. Prev. Med.*, 1932, 6, 321) made a study of New York City's mortality statistics to determine the truth of the statements that there has been an "appalling increase in the death rate of heart disease." The character of the basic data (death certificates) is analyzed and sources of errors to be guarded against are pointed out. The difficulty of classifying deaths in which there is more than one cause of death is discussed, and the practice of statistical offices is described. The pathologic changes and the etiologic factors in heart disease are shown not to be limited to the heart, but to include also the arteries and kidneys. The *registered* increase in heart disease is admitted and shown to be accompanied in New York City by a registered decrease in apoplexy, Bright's disease and deaths charged to senility. Statistics are presented which show that in New York City, for the population as a whole, the death rate from cardio-arterio-renal disease is no higher now than it was 30 years ago. Similar statistics are presented for the four important age groups, and only in the group aged 65 years and over do these show any increase in the death rate from cardio-arterio-renal disease.

Typhus Fever. The Multiplication of the Virus of Endemic Typhus in the Rat Flea *Xenopsylla Cheopis*.—DYER and his associates (*Pub. Health Rep.*, 1932, 47, 987) show by inoculation tests on guinea pigs that the virus of typhus multiplies enormously in fleas. While the whole of a recently infected flea might contain enough virus to infect a guinea pig one day after the flea had taken an infective feeding, after an interval of 40 days 1/128000 part of a flea was sufficient, showing enormous multiplication of the virus.

The Experimental Transmission of Endemic Typhus Fever of the United States by the Rat Flea *Ceratophyllus Fasciatus*.—DYER and his associates (*Pub. Health Rep.*, 1932, 47, 931) had previously shown that two species of rat fleas, *Xenopsylla cheopis* and *Ceratophyllus fasciatus*, were incriminated in the transmission of typhus from rat to rat and from rat to man. In the present report this latter named flea, *C. fasciatus*, is definitely proven to have carried the infection. The evidence is fortified by clinical, cultural, microscopic, serologic, pathologic, and cross immunity tests.

The Standardization of Scarlet Fever Streptococcus Antitoxin. A Method Employing the Ear of the White Rabbit.—VELDEE (*Pub. Health Rep.*, 1932, 47, 1043) undertook a study to determine the feasibility of using a laboratory animal in place of human subjects for the titration of scarlet fever antitoxin. The test worked out is performed in white rabbits, the inner side of the ear being utilized. An especially prepared and purified toxin of the scarlet fever streptococcus is used. Antitoxin prepared by using different antigens gave rather varying results in the tests, as is also the case when human test subjects are used.

Flocculating Tests for the Differential Diagnosis of Smallpox and Chickenpox.—HAVENS and MAYFIELD (*J. Infec. Dis.*, 1932, 50, 242) found flocculation tests with 38 serums in 35 cases of smallpox to give positive results with all but 5. Four of these negative specimens were taken during the first week of the disease. Two cases in which successive specimens were obtained showed an increase in titer during the course of the disease. Eight serums in 7 cases of chickenpox gave negative results. Flocculation tests with smallpox scabs and immune rabbit serum gave definitely positive results with dilutions of the antigens as high as 1 to 2000. Chickenpox scabs invariably failed to flocculate in dilutions higher than 1 to 500. The flocculation obtained with lower dilutions of the chickenpox antigens occurred also with normal rabbit serum, and its nonspecific character was further demonstrated by absorption of the serum with staphylococci present in the scabs.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 16, 1933.

Some Studies on Peptone.—CARL J. BUCHER (Laboratory of Bacteriology, Jefferson Medical College). 1. A chemical analysis was made

of five brands of commercial peptone, designated B, W, P, F, and C., to determine the total nitrogen, nonprotein nitrogen, protein nitrogen, polypeptid nitrogen, amino-acid nitrogen and ammonia, the chlorid content and reducing substances (sugar). Peptone B contained the largest amount of total nitrogen, polypeptid nitrogen, nonprotein nitrogen, and the least amount of protein nitrogen. Peptone W contained the least amounts of total nitrogen, nonprotein nitrogen and polypeptid nitrogen, but the largest amount of protein nitrogen. The other three gave values between the two in the following order: C, F, and P. All contained chlorid. C and P peptones contained large amounts. B, C, and F contained reducing substances (sugar?).

2. Five media were made, each containing 20 gm. of one of the peptones, and enough of dibasic sodium phosphate, monobasic potassium sulphate to the liter, to give a pH value of 7.2 to 7.4. One cubic centimeter of a dilution of *Bacillus coli* containing equal numbers of organisms was seeded in each of 50 cc. portions of the five media. By dilution and plating, the growth curves for 24 hours on the five samples were made. The results were that in the W medium growth was slower but more abundant than in the others. The peak was reached about the 15th hour. In the F peptone medium there was a marked decrease in the number of the organisms in the 1st hour. The maximum growth was reached about the 11th hour in the B, P, F, and C media. The numbers of bacteria in the other four media at the maximum period of growth were between $10^{10.5}$ and 10^{11} .

3. Indol production on four strains of *Bacillus coli* was studied in samples of the peptone media after a 48-hour growth period. The F peptone medium gives the best positive test with vanillin and hydrochloric acid. B and P give results inferior to F, but superior to W. With non-indol-formers P and B give strongly positive tryptophane reactions.

4. Gas production on the several media was tested with one strain of *Bacillus aerogenes* and four strains of *Bacillus coli*. Gas was produced in small amounts in the *Bacillus aerogenes* culture and with three strains of *Bacillus coli* at the end of 48 hours.

5. Variations in the production of pigment by a number of chromogenes in the several media, in a 72-hour period, was not significant.

Changes in Blood Concentration Incident to Shock.—V. H. MOON and PATRICK J. KENNEDY (Laboratory of Pathology, Jefferson Medical College). Monographs on clinical pathology and microscopy contain no references to blood changes in traumatic shock or circulatory failure of similar character. Occasional references to such changes are found in clinical reports, but their significance and diagnostic importance have not been emphasized.

Observations by Cannon, Fraser, Hooper, Keith and others on wounded soldiers showed an increase in red cell count and hemoglobin and a decreased total blood volume due to loss of plasma, accompanying the development of shock. We verified this observation in experiments on dogs. Increased concentration of blood was found so regularly that it was employed as a criterion for shock in experiments already published.

Krogh, Lewis and others have shown that many types of capillary injury result in loss of tonus and increased permeability. Agents

such as light, heat, many organic and inorganic chemicals, bacterial products and products of cellular injury similar to histamin, will produce such capillary damage. Any of these appropriately applied will produce the shock syndrome. There is low temperature and blood pressure, rapid weak heart action, rapid respirations and death by circulatory failure. At postmortem there is marked capillary congestion of the viscera, especially in the pulmonary and gastrointestinal tracts, edema and petechial hemorrhages. Shock is due essentially to loss of capillary tonus.

We have observed the physiologic disturbances and postmortem changes characteristic of shock, in poisoning with barbitol and other drugs, in mesenteric thrombosis, in influenza and other severe infections, in acute hemorrhagic pancreatitis, following burns and other severe intoxications. We have produced shock in dogs by various methods. In all instances there is a marked increase in the concentration of the blood as shown by specific gravity, red cell count and hemoglobin content.

Underhill emphasized increased concentration of blood as a feature of severe influenza, war-gas poisoning and of severe burns. De Takats and Mackenzie found it in 9 cases of acute hemorrhagic pancreatitis and proposed it as a test indicating the presence and the degree of shock.

Our observations indicate that circulatory failure resembling shock may develop in a wide variety of clinical conditions. An increased concentration of the blood, as shown by cell count, hemoglobin percentage and specific gravity, suggests that it is due to the same mechanism as traumatic shock. These observations may be helpful in clinical studies.

The Susceptibility of the Omentum of the Rabbit to a Single Exposure to Roentgen Rays (400 R).—NICHOLAS A. MICHELS (Daniel Baugh Institute of Anatomy, Jefferson Medical College). The animals were sacrificed at intervals from 5 to 96 hours after external exposure over the omental area. Factors: 200 K.V. 30 ma., $7\frac{1}{2}$ min. S.T. 50 cm., field 6 by 8, filter 0.05 cu., 1 mm. al. The induced histologic changes were studied in whole-mount preparations of the omentum.

As a rule there occurred initial destruction of lymphoid cells, the duration of the degenerative phase varying from 5 to 45 hours after irradiation. Disintegration of lymphocytes and histiocytes occurred primarily in sites of their genesis, *viz.*, in milk spots, the process being accomplished by fragmentation of cytoplasm, dechromatization, fragmentation and dissolution of chromatin. The cellular debris was disposed by macrophages, many of which were of local origin, including mesothelium.

In early stages after irradiation (5 to 18 hours), omental capillaries were engorged with polymorphonuclear cells, a vast number of which migrated into the tissues where they disintegrated, presumably liberating a defense substance. Comparable extensive leukocytic infiltrations occurred in the lymph nodes and spleen.

Hemorrhages in omental capillaries occurred both in early (18 hours) and in late stages after irradiation (65 hours). Massive or diffuse in character, they were always accompanied by extensive blood stasis, agglutination of red cells, tortuosity, occlusion and degeneration of

capillaries. At times the capillary tortuosity was so pronounced that it led to the formation of broad blunt capillary stubs, which after being severed from the capillary bed constituted solid round capillary knots, the constituent cells of which degenerated.

Many instances of impairment and complete abolition of function in entire capillary tuft formations occurred 18 hours after irradiation, the endothelial cells of the peripheral capillaries dedifferentiating in mesenchyme.

The stimulating effect of a single small dose of Roentgen rays on lymphoid tissue manifested itself as early as 1 day after exposure and after 3 days reached such magnitude as to convert the omentum into a highly organized lymphoid organ in which the capillary vascularization was likewise enormously increased. By mitotic and amitotic proliferation the local mesothelium gave rise to 4 types of lymphoid follicles, *viz.*, solitary follicular, adventitial and mixed forms, many of which measured from 1 to 3 mm. in diameter.

A constant effect was the production of fibrosed areas in the omentum. Minimal after 5 hours, the process of fibrosis assumed larger proportions after 25 hours, was very pronounced and extensive after 65 to 77 hours and attained maximal density from 91 to 96 hours after exposure. Cell factors responsible for the fibrosis were primarily fibroblasts and mesothelium, secondarily endothelium and free lymphoid cells, including lymphocytes. Wide extension of a close-meshed capillary network was often the forerunner of fibrosis in the sense that after cessation of the circulation the constituent endothelial cells became fibrillogenetic. These experiments provide confirmative evidence of the generally accepted biologic law that each variety of cell has a specific and selective sensitiveness to irradiation. The order of radiosensitiveness displayed by the omental connective tissue cells was as follows: lymphocytes, pseudoeosinophils, eosinophils, plasma cells, monocytes, endothelium, pericytes, fat cells, polyblasts or histiocytes, fibrocytes, mesothelium, mast cells, the latter being the most radioresistant, as their morphology was unaltered 91 hours after irradiation.

Opposed to Desjardin's recent contention that all stimulative changes induced by irradiation are essentially defense reactions or compensatory in character, this study shows that a single small dose of Roentgen rays causes a primary and direct acceleration of cellular metabolism on the omental cells.

Arterial and Venous Blood Sugar Response to Epinephrin in Normal Individuals and in Biliary Tract Disease.—A. CANTAROW (Laboratory of Biochemistry, Jefferson Hospital). This report consists of a study of the relationship between the concentration of glucose in capillary and venous blood before, and $\frac{1}{2}$, 1, $1\frac{1}{2}$ and $2\frac{1}{2}$ hours after the intramuscular administration of 15 minims of epinephrin to 33 individuals with and without disease of the liver and biliary passages. In each instance the fasting cutaneous and venous blood sugar concentrations were practically identical and were well within normal limits. The following changes occurred following the administration of epinephrin:

1. *Normal, 16 Cases* (no evidence of organic disease). Average maximum rise above resting level: (1) Capillary blood, 62 mg. per 100 cc.; (2) venous blood, 44 mg.; (3) arterial-venous difference, 31 mg.

2. *Catarrhal Jaundice, 4 Cases.* Average maximum rise above resting level: (1) Capillary blood, 29 mg. per 100 cc.; (2) venous blood, 24 mg.; (3) arterial-venous difference, 9 mg.

3. *Catarrhal Jaundice, Recovered, 3 Cases.* Average maximum rise above resting level: (1) Capillary blood, 61 mg. per 100 cc.; (2) venous blood, 38 mg.; (3) arterial-venous difference, 23 mg.

4. *Carcinoma of Liver, 4 Cases.* Average maximum rise above resting level: (1) Capillary blood, 14 mg. per 100 cc.; (2) venous blood, 11 mg.; (3) arterial-venous difference, 3 mg.

5. *Hepatitis, 2 Cases.* Average maximum rise above resting level: (1) Capillary blood, 16 mg. per 100 cc.; (2) venous blood, 11 mg.; (3) arterial-venous difference, 5 mg.

6. *Portal Cirrhosis, 3 Cases.* Average maximum rise above resting level: (1) Capillary blood, 22 mg. per 100 cc.; (2) venous blood, 18 mg.; (3) arterial-venous difference, 8 mg.

7. *Cholecystitis, 1 Case* (no jaundice). Average maximum rise above resting level: (1) Capillary blood, 17 mg. per 100 cc.; (2) venous blood, 12 mg.; (3) arterial-venous difference, 8 mg.

In the normal individuals and in those with catarrhal jaundice the maximum capillary and venous blood sugar levels were reached within 60 minutes while in those with hepatic carcinoma and hepatitis they were not reached until 90 minutes following the injection of epinephrin.

The interpretation of these data is difficult. It appears to be rather definitely established that epinephrin increases the mobilization of hepatic glycogen and decreases glucose utilization in the muscles and that normal epinephrin hyperglycemia results from the initial, transient hepatic glycogenolysis and is maintained by the decreased glucose utilization in the muscles. The subnormal blood sugar rise in hepatic disease may be due to either an insufficient quantity of glycogen in the liver or an increased tolerance to epinephrin. The subnormal arterial-venous difference may be due either to decreased glucose utilization in the muscles or to the relatively slight increase in the arterial blood sugar concentration, possibly below that required for the stimulation of active glucose utilization in the tissues.

Introduction to the Study of Purpura.—*A. Experimental Production of the Reactive Stage.* HAROLD W. JONES and LEANDRO M. TOCANTINS (Department of Medicine, Jefferson Medical College). From our studies of a large group of patients with purpura, we believe that all types are fundamentally similar, varying in degree of symptomatic expression only. Easy bruising, plus epistaxis, plus petechia, plus menorrhagia in normals may be related to acute purpura.

The fundamental pathologic factors in purpura are:

1. Mucous membrane disease.
2. Altered capillary hyperpermeability or fragility.
3. Platelet deficiency.

The contributing factors are:

1. Infection (tuberculosis and tonsillitis).
2. Glandular dysfunction (ovary and pituitary).
3. Toxic effects (heavy metals—disease as chronic nephritis, etc.).
4. Vitamin deficiency.
5. Allergy.
6. Heredity.

Platelet number, bleeding time length and development of hemorrhagic phenomena are variables which require experimental explanation. Clinical spontaneous cure is frequently seen. A great number of substances, such as iron, distilled water, etc., and methods such as purging, laying on of hands, anointing with holy water and hexing have produced such a cure.

Experimentally we were able for the first time to produce active purpura in dogs with as little as 1 cc. of antiplatelet serum injected either subcutaneously or intraperitoneally. All hemorrhagic features seen clinically have been observed in our animals with the exception of epistaxis. Skin petechia, ecchymosis, hemorrhage from the bowel, hematuria, hemorrhage into the peritoneum, iris, into the mucous membrane of the mouth, and conjunctival hemorrhage have been seen. Capillary resistance test and flicking test are positive. Bleeding time is greatly lengthened and the platelets are reduced.

Reactive Stage. Thirteen cubic centimeters of antiplatelet serum are injected either subcutaneously or intraperitoneally over a period of 13 days. Purpuric phenomena are present continually. Twenty-four to 48 hours after the last injection the hemorrhagic phenomena disappear. Following this there is a gradual platelet increase until the normal number is doubled, usually well over a million. At the height of the reactive stage, which varies in different dogs, and which may come at any time from 3 to 7 days after the last injection of antiplatelet serum, these phenomena are observed:

1. Inability to get blood for bleeding time by usual method.
2. Six to eight punctures must be made in order to obtain sufficient blood for red cell count.
3. There is hypereagability of the blood.
4. Rapid agglutination of platelets.
5. Tonicity of the skin is greatly increased.
6. Marked paling of mucous membranes of mouth and conjunctiva, probably due to capillary contraction.

The intensity of these phenomena gradually disappears over a period of 4 to 5 weeks. It is impossible during this reactive stage to produce purpura by the usual injections of antiplatelet serum.

We feel that the phenomena observed in this stage probably explain the development of the clinical spontaneous cure. An understanding of the mechanism of the production of the reactive stage will go far towards solving the problems surrounding the etiology and treatment of purpura.

Variations in Platelet Behavior After Intravenous Injection of Antiplatelet Serum in Dogs.—L. M. TOCANTINS and H. W. JONES (Department of Medicine, Jefferson Medical College). An antiplatelet serum was prepared by a series of injections of emulsions of dog's platelets into a rabbit. One cubic centimeter of this serum was injected intravenously into dogs weighing between 6.6 and 8.6 kilos, between 6 and 11 months of age. The platelets dropped below 50,000 within a few minutes and remained low for 48 hours. The animals developed purpura. The platelets began rising by the end of the second day and were back to normal 5 days after the injection. The curve of regenera-

tion of platelets after their destruction by antiplatelet serum follows very closely the curve found by Duke (1911) after almost complete defibrination of the blood of young dogs.

When the same dose of the serum was given to dogs that had received previous injections of the serum and had had purpura, no purpura was developed and the platelets rose from 68,000 to 500,000 2 hours after the injection and continued to rise. They reached their previous level of 950,000 in 3 days and climbed up to 1,170,000 9 days after the injection, then returning to normal.

The same dose of the serum was given to a dog with the spleen extirpated. During the period when the platelets in the blood from the ear vein were at their lowest, the spleen showed strong contractions and was reduced to approximately two-thirds of its previous size. The platelet counts obtained by splenic punctures were higher by 100 to 200,000 during the strongest contractions. When the spleen enlarged again, the reverse took place. No purpura developed.

Conclusion. In dogs that have been prepared by previous injections of antiplatelet serum, the lowering of the platelet level by injection of 1 cc. of this serum intravenously is followed by a rapid regeneration of the platelets and reestablishment of a normal level in a few hours. This response may be partly due to splenic action, but is probably dependent more on an increased ability of the previously injected animals to recuperate from destruction of their blood platelets. The animals that so behave are in the reactive stage and do not show purpura after doses of the serum, enough to produce purpura in similar animals not in that stage.

The intravenous injection of 1 cc. of antiplatelet serum, in not previously injected animals, constitutes a good method for the estimation of the value of therapeutic measures intended to influence the course of purpura, since all such animals behave alike after the injection insofar as the blood platelets, capillary resistance and bleeding time are concerned.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1933

ORIGINAL ARTICLES.

I. A CLASSIFICATION OF THE DISEASES OF LIPOID
METABOLISM AND GAUCHER'S DISEASE.*

BY PROFESSOR LUDWIG PICK,
BERLIN, GERMANY.

(From the Pathological-Anatomical Institute, Municipal Hospital, Friedrichsheim.)

THE concept of xanthomatosis includes a series of clinical and anatomic conditions in which lipoid substances are deposited in certain tissue systems or organs of the body, thus producing a yellow discoloration of these tissues or organs. There exist, however, certain doubts concerning the desirability of this designation. First of all, the expression is misleading insofar as the word xanthoma contains the ending "oma" and leads one to think of a neoplasm, which is true only for certain isolated cases of xanthomatosis. Second, the term suggests the erroneous idea that the deposited lipoids are all of a certain type. On the contrary, in the various forms of xanthomatosis the lipoids occur in quite different forms and, therefore, by no means always produce the same yellow discoloration of the affected zones. As there is no uniformity in the nature of these deposits, the term is wrongly used to designate the entire group of these diseases. Also in the diffuse skin xanthomatosis of diabetes the color is produced by the so-called lipochromes contained in neutral fat and not related to lipoids. However, as it would be difficult to eradicate this firmly established word and to replace the term "xanthomatosis" by the much more suitable

* The first of the eighth series of Dunham lectures delivered at the Harvard University Medical School, May 3, 1932.

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term "lipoidosis," in the further analysis and classification of the xanthomatoses, we must attempt to make up by strict precision for the lack of accuracy in the general term.

Classification of Xanthomatoses. We first divide the xanthomatoses into two groups, namely, generalized and localized. The generalized forms consist of: (1) the symptomatic or secondary forms, those which accompany other diseases and are symptomatic manifestations of disturbances of lipid metabolism associated with these diseases; (2) the essential or primary forms, those which constitute disease entities in themselves and are based upon a constitutional anomaly of lipid metabolism.

The following are examples of the symptomatic xanthomatoses: Multiple or generalized xanthomata (or xanthelasmas) in diabetes or in liver diseases which are associated with jaundice and in chronic kidney disease. They occur as pea or bean-sized yellow or brown deposits or nodules in the skin. They are generally flat; the larger ones may sometimes be tuberosus and are often surrounded by a hyperemic zone. They are found especially on the extensor surfaces of the extremities, notably about the elbows and the knees.

In these lesions the lipid is deposited mainly in proliferating cells of the connective tissue of skin and in the endothelium of lymph vessels. The tremendously enlarged cells contain closely packed droplets and needles which consist of a cholesterol fatty acid ester. They stain with Sudan and are doubly refractile. When the lipoids are extracted by alcohol in the microscopic section large foam cells can be observed. In diabetes, as well as in cases of jaundice, the substances which are deposited in the xanthoma cells (cholesterol fatty acid ester) appear in the blood stream in an increased and often considerable quantity. In 1906 I, therefore, explained the symptomatic xanthomatosis in these diseases on the basis of a cholesteremia and a selective absorption of the cholesterol fatty acid ester by the xanthomatous cells. In this way it is easy to understand the recurrent eruptions and the transitory character of these lesions. In some cases the cells of the internal organs also take part in this cholesterol fatty acid ester storage, thus giving rise to a form of a visceral xanthomatosis. In 1 of my cases, for instance, after jaundice of long duration due to liver cirrhosis, a pachymeningitis interna xanthomatosa was found. Sometimes when a diabetic patient with lipemia dies in coma the spleen may be affected in a characteristic manner, in addition to the lipid deposits which may be present in the skin, the lymphatic and hematopoietic systems, the suprarenal cortex, the intima of the aorta and the endocardium. The spleen in such cases may be twice the normal size and weigh 450 gm. The pulp may be completely infiltrated with large clear cells which, according to the variable character of the lipemia, probably represent a mixture of neutral fats, phosphatids and cholesterol fatty acid esters. The

inclusions, according to their chemical character, give the well-known microchemical reactions for fat and lipid substances in varying degrees. In the microscopic section of such a spleen, the large phagocytes appear as distinct foam cells. It is noteworthy that they spring entirely from the reticulum cells of the pulp. The endothelial cells of the splenic sinuses are entirely unaffected even when they are situated in the midst of large accumulations of foam cells.

The variability in the character of the intracellular lipoids in such a spleen forms a definite contrast to the uniformity of the cholesterin-fatty acid esters in the diabetic xanthomatoses of the skin or inner organs. However, the difference in the distribution of the deposition of lipoids easily explains this. The faster the lipemia develops, the greater is the variability and the less is the purity of the accumulated substances.

Conversely, in the usual subchronic form of diabetic xanthelasma, the picture in the spleen is less prominent and the character of the deposited substance is more pure and uniform. We then find cholesterin fatty acid esters.

We next consider the essential or primary xanthomatoses. Only the researches of the last decade have cleared away much confusion and a number of precise pathologic entities have emerged which can be well differentiated clinically and anatomically.

In this group belong: (1) Gaucher's disease, (2) Niemann-Pick's disease, (3) Hand-Schüller-Christian's disease, (4) the primary non-symptomatic external and internal xanthomatoses which occur in varying distributions and intensity in the skin and in the inner organs.

We are able to differentiate these diseases not only by their clinical and anatomic properties, but also according to the chemical character of the deposited lipoids. To a certain extent we can use for this purpose the microchemical properties of the lipid cell contents in addition to their morphologic and optical appearance. Cholesterin fatty acid esters are sudanophilic and doubly refractile. Phosphatids are blackened intensely by the Lorrain Smith-Deitrich method but they are optically inactive, while the lipid in Gaucher's disease cannot be stained at all and is not doubly refractile. Of course, it is recognized that the value of all microchemical tests is a very relative one. The lipoids in these cases are not in pure form but always in mixtures. Their staining properties are influenced by other substances in the cytoplasm and the specificity of the histochemical methods for differentiation of all fats depends upon the character of the mixture of fats or lipoids. We have, therefore, augmented the histochemical methods by exact chemical analyses of the affected organs. It was especially the Viennese pathologist, Epstein, who successfully showed that the deposited lipoids in the group of primary xanthomatoses are of various chemical natures.

It must be recognized, however, that his methods and results have not been wholly accepted.

A further step forward has been made by the observation that in certain disease groups, for instance, in Gaucher's disease and in the essential internal xanthomatoses which do not yet have a special name, the skeleton is affected to a prominent degree. There really are subgroups consisting of osseous forms with special chemical and roentgenologic pictures. In Hand-Schüller-Christian's disease the bone lesion is a regular and leading symptom.

Further attention has been paid to the relation between the primary xanthomatoses and the reticuloendothelial system of Aschoff, with its single cell forms as, for example, endothelial cells, reticulum cells, histiocytes, etc. Gaucher's disease has even been characterized as a disease of the whole reticuloendothelial system (Aschoff) while Niemann-Pick's disease has been designated a lipid histiocytosis (Bloom). You will see later that these designations are either too inclusive or do not designate the extent of the lesions.

Finally, investigation of the various types of the primary xanthomatoses has brought experimental lipid cell hyperplasia into prominence. These so-called exogenous cholesteroses have been produced experimentally by Chalatow, Anitschkow and Verse and their coworkers, by feeding lipid to animals.

The outstanding forms of essential xanthomatoses, namely, Gaucher's, Niemann-Pick's, Hand-Schüller-Christian's disease and the less regular forms, will form the main topic of my lectures.

The last group in the classification is composed of the localized xanthomatoses, that is, xanthomatous deposits in only one area of the body. They may be non-neoplastic in character. Of this group the xanthomata in the skin of the eyelids are the best-known form. They consist of circumscribed yellow spots or nodules. The localized xanthomatoses may be true neoplasms, xanthomatous blastomata, sarcomata or, less frequently, carcinomata. In each case accumulation of lipoids in the tumor cells produces the xanthomatous appearance. Recurrences of these tumors, however, are not at all different from ordinary carcinomata or sarcomata. Other authors and I have seen, for instance, metastasizing foam cell carcinomata of the prostate. A special circumscribed type of purely local neoplastic xanthomata is the *xanthoma en tumeurs* of the skin, found generally on the knee, the elbow or the heel. They consist of firm tumors up to the size of a hen's egg. Their cut surfaces are dull white or yellow, containing some gray or brown spots. These tumors originate in the subcutaneous tissue. They are cellular sarcoma-like tumors and the foam cells are packed with doubly refractile substances. The tumors otherwise contain many multinucleated giant cells and iron pigment. They recur locally but rarely are there distant metastases.

For all these local forms of xanthomatosis cholesterinemia has been postulated as a *conditio sine qua non*. Systematic examination will be necessary before we know whether this is a fact or whether nonspecific localized disturbances in the lipid metabolism of the tumor cells underlie this form of xanthomatosis.

Gaucher's Disease. We now turn to Gaucher's disease. This disease was described in 1882 by Gaucher as a primary epithelioma of the spleen; the disease is thus just 50 years old. In 1900 Bovaird, of New York, claimed that Gaucher's disease is non-neoplastic and is an endothelial hyperplasia in the spleen, liver and lymph nodes. In 1907 Schlagenhauser designated the disease as a systematic affection of the reticulum cells of all the lymphatic and hematopoietic organs, including the bone marrow. In the same year, 1907, Marchand recognized the importance of a deposit of foreign substance in the histogenesis of the Gaucher cells. Mandelbaum and Downey, in 1916, founded the modern conception of the disease as a metabolic disturbance, and in 1924 Lieb and Epstein, by chemical analysis of the spleen, demonstrated the lipid nature of the Gaucher substance. They show that kersin is its more important constituent. Kersin belongs to the cerebrosids (sphingogalactids). These facts give you a short history of the disease.

Gaucher's disease is not very rare. Since I started my investigations the number of cases reported in the international literature has rapidly increased to more than 75. It is congenital and familial in occurrence, since in about one-third of the cases several members of one generation are concerned, but the disease is limited to this generation only. About twice as many cases occur in females as in males. The enlarged spleen and liver may be noticed as early as the first months of life. The disease may lead to death in infancy. The symptoms are those of rapidly progressing cachexia, though the main symptoms may be cerebral with spastic paralysis and psychic disturbances. Generally, however, the large spleen is discovered accidentally in childhood. The enlargement of the liver usually occurs after the spleen has reached considerable size.

Furthermore the splenic and liver tumors show a progressive increase in size, although relatively the liver grows less rapidly than the spleen. The course is frequently quite chronic and in some cases extends over many decades. The oldest patient on whom I did a postmortem examination was 56 years. The organism, in this extraordinary duration of the process, adjusts itself to the organ changes. Even with the gigantic size of the spleen and liver the symptomatic disturbances are often strikingly slight. The superficial lymph nodes do not usually take part in the changes and are, therefore, as a rule, not palpable. Involvement of the bones in the usual case is noted by pains in the lower ends of the femur and tibia or by tenderness over the sternum and ribs.

As early signs are to be noted the characteristic pigmentation of

the skin and definite blood changes. The diffuse or spotty pigmentation, mostly confined to the face, neck and hands, shows a yellow brown to ochre tone. In addition there occur brownish-yellow wedge-shaped thickenings of the scleræ, the base of the wedge lying toward the margin of the cornea. All of these pigmentations are expressions of a general hemochromatosis which is constantly present in this disease and becomes more marked with increased duration of its course.

The blood changes consist first of a leukopenia which may be due to a diminution in polymorphonuclears or lymphocytes. Then there follows a moderate hypochromic anemia. At no time are there Gaucher cells present in the blood stream. Often one sees a thrombocytopenia early in the disease, related perhaps to the hemorrhagic diathesis which characterizes the late stages of the disease. Most often there is bleeding from the nose or gums and sometimes hematemesis, melena, uterine bleeding and hemorrhage in the connective tissue, muscle and skin, occasioned by slight trauma, may occur. Death is only rarely the sequel of cachexia or rapidly progressive anemia; more usually it is due to intercurrent diseases, such as pneumonia, sepsis, tuberculosis, carcinoma, etc., and in infants to bronchopneumonia. Patients may die following splenectomy.

In a clinical differential diagnosis one must consider splenic anemia, Banti's disease, familial splenomegaly, acholuric icterus (hemolytic icterus) and Hanot's biliary cirrhosis. There is no pathognomonic clinical symptom but we possess a simple and excellent diagnostic aid, namely the microscopic examination of material from a puncture of the spleen or of bone marrow obtained from the tibia or sternum. The material obtained on puncture always shows in fresh or stained smears the large characteristic Gaucher cells. Occasionally one can demonstrate even in the minutest particles obtained on puncture the specific tissue structure of the Gaucher spleen.

GROSS PATHOLOGIC ANATOMY. The picture is frequently dominated by the extreme enlargement of the *spleen* which may weigh as much as 8100 gm. In 24 cases in adults I found an average splenic weight of 2700 gm. (compared to about 250 gm. normally); in 7 cases in children between the ages of 5 and 14 years, the average weight being 1800 gm. The organ is very firm and tough and shows on cut section a very characteristic appearance. The reddish-gray, pink or sometimes chocolate-brown background is always thickly stippled with innumerable gray-white or gray-yellow markings which close in to form a fine anastomosing network. They correspond to accumulations of Gaucher cells.

A second common characteristic of the Gaucher spleen is formed by larger or smaller nodular cavernous foci which are always multiple, and which occur only rarely in the normal spleen. Its dark

red surface on section shows thick blood-filled dimples or meshes. As a result of organization, they are transformed into globular, solid, calloused, fibrous nodules. Other irregular fibrotic foci correspond to a scarlike substitution of masses of Gaucher cells and still other foci represent scarred anemic or hemorrhagic infarcts.

A liver weight of 3300 gm. in 7 cases in adults (in comparison with 1500 to 2000 gm. normally) shows marked enlargement but the increase in weight of the liver is relatively less than that of the spleen. Interspersed in the brownish-red, yellowish or chocolate-brown parenchyma of the liver there can be seen small pale spots or conglomerated areas not unlike leukemic infiltration (Fig. 1). At other times there is a cirrhosis-like picture, without the usual changes found in cirrhosis.

Much less significant are the changes in the *lymph nodes* and in the *bone marrow*. The superficial lymph nodes, as I have already said, remain normal in size; the intraabdominal and intrathoracic glands, although almost always involved, hardly ever reach the size of a walnut (2 cm. in diameter) and are at the same time colored more or less brown by heavy deposits of pigment. Grossly the bone marrow is either entirely unchanged, or, like the spleen and liver, shows whitish, spotted deposits.

As signs of *hemachromatosis*, which belongs to the anatomic and clinical picture of Gaucher's disease, I have already mentioned the yellowish-brown discolorations of the skin and sclera, and the occasional chocolate-brown color of the parenchyma of the spleen, liver and lymph nodes. The wall of the uterus and the mucous membrane of the uterus, stomach and intestines also may be involved. In all these cases of pigmentation one must always determine whether the pigment has merely originated from a local hemorrhage which may occur as an expression of a widespread hemorrhagic diathesis.

PATHOLOGIC HISTOLOGY. The study of the Gaucher cells concerns, first of all, the *spleen*. The whitish spots correspond to foci of Gaucher cells, mostly sharply confined in alveolar fashion (Fig. 2) which are more or less thickly interspersed in the parenchyma of the spleen. Only rarely are they spread diffusely. In fresh specimens the Gaucher cells are homogeneous, opaque, dull-hyalin in appearance. With the Mallory stain, with acid-fuchsin, anilin-blue-orange G, and with previous fixation with picric acid and ammonium bichromate, they appear a light blue, and under higher magnification show, in their cytoplasm, an irregular network, bound like spider webs with the finest thread-like fibrils. Through these the cytoplasm appears wrinkled rather than foamy or roundly vacuolated. The wrinkles correspond to the remains of the spongiosum in whose meshes the Gaucher substance is stored. Large cells with this type of cytoplasm are found in no other affection. The cells measure from 20 to 80 μ in their largest diameter; they

are polymorphous and often furnished with projections. The nuclei are either single or multiple and not infrequently are quite numerous. I have counted as many as 21 in a single cell. They are most often pyknotic. In those cells where there is a single nucleus, it is often eccentric in position, generally near the cell border. Mitoses are disputed (Figs. 3 and 4).

An important finding which I have regularly observed in my examinations that seems to have completely escaped previous observers consists of arterial branches within the nests of Gaucher cells. They lie in part centrally, in part eccentrically. They occur most often singly but they may be double or appear as a main stem with branches (Fig. 5). The intima and media are always intact as are usually the innermost cells of the adventitia.

The Malpighian bodies remain quite passive. They may be replaced by Gaucher cells.

Pigment is absent only in children and infants, otherwise it is present without exception and increases in quantity with increased duration of the disease. It is, as the Turnbull reaction shows, mostly hemosiderin. Aside from the cells of the splenic trabeculae, it is present in the endothelial cells of the venous sinuses and in the Gaucher cells themselves.

There is a second noteworthy finding which I was able to demonstrate in the spleen. In all the cases of Gaucher's disease which I examined I found the endothelial cells of the venous sinuses containing hemosiderin, without exception, but no Gaucher substance. The Gaucher cells contained in many cases no hemosiderin at all; at other times there was either slight or more marked diffuse hemosiderosis. In every instance, however, they were far poorer in their hemosiderin content. Erythrophagia on the part of the Gaucher cells may occur, but is not the rule.

Bone marrow giant cells, megakaryocytes, which occur in the Gaucher cell alveoli as well as in the pulp of the Gaucher spleen, indicate foci of blood formation. Near them one finds the usual elements of hematopoiesis.

The blood spaces of the cavernomata are lined by a simple endothelium containing large amounts of hemosiderin. This is regularly interrupted by groups of Gaucher cells from the periphery or from the septa. Except for the Gaucher cells, these spaces frequently contain all the elements of myelopoiesis (Fig. 6) in addition to intracellular or extracellular blood pigment. Nearby there are miniature cavernomata, that is, groups of cavernous vascular dilatations of microscopic size. In some Gaucher spleens these are the only kind of cavernoma and occur in very large numbers.

Of special histologic interest, finally, is the disappearance of the Gaucher cell parenchyma which, as I have already said, results in calloused, fibrotic nodules. The Gaucher cells are not destroyed by fatty degeneration, caseation or a special type of degeneration.

Rather, the simple necrotic or atrophic cells disappear by a gradual diminution in size and simultaneously there develops intercellularly a firm connective tissue, whose meshes develop into fibrotic nodules.

In the *livers* of infants and young children the Gaucher cells are found exclusively in the capillaries. In older children and in adults the Gaucher cells help produce a peculiar cirrhotic thickening of Glisson's capsule and disintegration of liver lobules (Fig. 7).

This process is distinguished from the usual liver cirrhosis by the following characteristics:

1. The cirrhotic connective tissue contains always small nests of Gaucher cells, generally in large numbers. The Gaucher cells have here a distinct tendency to stretch, to arrange themselves in bundles and form syncytia. Each cell lies in a reticular mesh.

2. In contradistinction to ordinary cirrhosis, there is no antecedent granulating proliferation which causes the production of connective tissue.

3. Bile duct proliferation is generally lacking.

As in the spleen, the pigmentation in the liver increases during the course of the disease. In later stages there is always hemosiderin in Glisson's capsule, but the Gaucher cells in the latter contain hardly any pigment.

In the *lymph nodes* the capsule and the trabecular system become markedly thickened and the lymphadenoid parenchyma is replaced by Gaucher cells which lie in individual meshes of fibrous tissue. There is, however, no characteristic relationship of the lesions to the degree or the duration of the disease. The amount of pigment—generally and predominantly hemosiderin—is usually higher than in spleen and liver.

The *bone marrow* shows a number of peculiarities, even in those cases of Gaucher's disease where it is not prominently involved.

1. There is, as in the lymphatic system, no direct relation between the intensity of the Gaucher cell deposits and the duration of the disease. The whole skeleton may be affected in a year-old infant.

2. There are marked variations in the amounts of Gaucher cells deposited in the individual bones, and in the particular form of storage. At times we find the Gaucher cells quite diffusely scattered; at other times in poorly delimited confluent foci, and then again only in small cellular nests or isolated collections.

3. Brill, Mandelbaum and Libman have already shown the peculiar tendency of Gaucher cells in bone marrow to stretch and change their configuration. These elongated and frequently spindle-shaped cells are distinctly wrinkled or finely fibrillar and striated. Delicate connective tissue and reticulum fibers course between the single cells, often intimately fused with the periphery of the cell. Here also the gradual disappearance of Gaucher cells due to atrophy and necrosis and the concomitant thickening of the intercellular fibrous network may cause the development of large calloused foci.

Finally, the pigmentation in the bone marrow, as in other organs, is irregular and insignificant.

The pigment of Gaucher's disease is predominantly hemosiderin as far as the hematopoietic and lymphatic system is concerned. Iron-free pigment, originating from protein, plays a lesser rôle, but is found occasionally in large amounts outside of the hematopoietic and lymphatic apparatus, in smooth muscles of the intestines, stomach, uterus or in voluntary musculature; furthermore, in the vascular wall and in connective tissue in these and other locations. Autogenous pigment also causes the brown discoloration of the skin, according to my investigations. All these iron-containing and iron-free pigments are expressions of the general hemachromatosis, *i. e.*, increased blood destruction.

Do Gaucher cells occur outside of the above-mentioned organs of the hematopoietic, lymphatic and vascular system? Do organs, other than the spleen, the liver, the lymph glands and bone marrow, contain Gaucher cells?

The answer to these questions is in the affirmative, if applied to cases of Gaucher's disease in infants. Histologic study has demonstrated the presence of unmistakable Gaucher cells in the thymus, tonsils and the lymphatic apparatus of the intestine, perhaps also in the lungs. But there is a very plausible explanation for these exceptions. Lubarsch's investigations on the phagocytosis of iron pigment and fat in infants have shown that the potency of phagocytosis of certain cell groups of infantile organs changes about at the end of the first year. By that time cells capable of storage up to that time (the reticulum cells of the thymus, the perivascular cells of the suprarenals, the lymphoreticular cells of the intestine or of the tonsils) lose their phagocytic capacity. Therefore, you may find Gaucher cells in infants, in places where they are missing in the adult.

Two findings represent the essential morphologic characteristics of Gaucher's disease:

1. The large cell infiltration limited to the spleen, liver, lymph glands and bone marrow.

2. The peculiar morphologic type of the Gaucher cell, particularly the character of the cytoplasm. Certainly the Gaucher cell is the proper morphologic representative of Gaucher's disease.

According to newer investigations in infants, it seems that the Gaucher substance may be stored in additional places, for instance, in the pyramidal cells of the cerebral cortex. Such changes have been first pointed out by Oberling and Woringer. They describe a "progressive cortical atrophy." Lindau, a Swedish author, has lately shown that the changes in the ganglion cells and their dendrites resemble morphologically those found in the familial amaurotic idiocy of Tay-Sachs. They provide a very plausible explanation for the psychic disturbances and the spastic paralysis

to which these infants succumb. The inclusion in the ganglion cells and their dendrites are microchemically inactive, as is the Gaucher substance itself. Whether this change is a regular occurrence in Gaucher's disease of infancy remains as yet unproved.

If, as we have seen, the Gaucher cell is the morphologic pathognomonic sign of Gaucher's disease, then there arises the question, What is *the substance that causes the peculiar appearance of the Gaucher cell?*

As I said previously, the Gaucher substance is optically and microchemically inactive. Mandelbaum's dictum that a microchemical finding of neutral fat, myelin-like or doubly refractile substance in suspicious cells excludes the presence of Gaucher's disease still holds true. The problem can only be solved by chemical analysis of the organs.

Lieb and Epstein succeeded in finding the solution of the problem. According to their results, the Gaucher substance is essentially kersin which belongs to the cerebrosids. Such large amounts of it are stored in the Gaucher spleen that they may comprise up to 10 per cent of the dried spleen. Epstein finds in addition to kersin only alcohol (not ether) soluble phosphatids in the mass of the Gaucher cell complex. Kersin precipitates from solutions in diluted alcohol in the form of needle-shaped crystals, which aggregate in characteristic spherical and rosette-like configurations (Fig. 8).

As you have heard, autopsy on the newborn shows that at this time the Gaucher cells are found in the spleen, liver, lymph nodes and bone marrow. In addition, contrary to previous views, one sees that the process in the spleen, liver, lymph nodes and bone marrow is a diffuse one from the very onset, even though the spleen dominates the pathologic and clinical picture. The enlargement of the liver may not follow until later. From this it follows that it is only the rapidity of growth which is of interest in the further development of the disease.

OSSEOUS TYPES. This "participation curve" of the organs in Gaucher's disease may be altered in an extraordinary way. There is a form that is clinically and anatomically preponderantly osseous. Here one must assume a special constitutional redispotion of the skeletal system, and this is supported by the observation that at times all the affected members of a Gaucher family in one generation may have the osseous form of the disease. In these cases two related constitutional deficiencies must be at play—the one, the predisposition to Gaucher's disease in general, the other a special localization in the skeletal system as a manifestation of a particular deficiency of the mesenchyma. I have seen this in 5 brothers, on 2 of whom I was able to carry out complete autopsies and histologic investigations of the skeletal system. These osseous cases where the process is so generalized in the skeletal system that scarcely a bone is spared give the disease a completely altered clinical aspect.

These may remain unrecognized during life and be regarded and treated as tuberculosis or syphilis of the bones. The localization in the skeletal system, as we learn from the postmortem examination, is not only absolute but also relative, that is, the weight of the spleen and liver, despite the predominant involvement of the bones, is less than the average weight of these organs in Gaucher's disease. In the small and flat bones, for example, in the calvarium, the markedly porous spongiosa is filled with a yellow or gray deposition, either diffusely or in a speckled form. This diffuse or speckled form is also the prototype of both forms which occur in the marrow cavity of the long bones. In the marrow cavity nodules of the size of a walnut lying close together partly encapsulated with fibrous tissue more or less pigmented, sometimes hemorrhagic or scarred, are conspicuous and reveal with the still remaining yellow or gray-red marrow rests, a strikingly variegated picture (Fig. 9). A diffuse tough mass may fill the marrow cavity like a plug, broken up partially by the still intact marrow substance (Fig. 10). It is sharply defined from the compact bone by a thick, pale, partially osseous boundary. The cortex appears coarsely vacuolated and may be very thin. The cortical vacuoles and cavities are filled with yellow and red tissue. The infiltrating Gaucher cell masses can cause swelling of the bones, for instance, in the lower femur and the upper third of the tibia. The much thinner compact bone naturally may be subjected to spontaneous fracture. Invasion of the head of the femur, with depression fracture and resulting deformity, leads to a deforming arthritis of the hip joint. This is the cause of irreparable limping. Especially severe changes result from the complete Gaucher infiltration of the vertebræ. They are reduced to one-half or even one-third of their normal size (Fig. 11). The body length is correspondingly shortened. In the lower dorsal or upper lumbar regions some of the vertebræ are crushed into a mortar-like mass. A gibbus results. The neighboring vertebræ or intervertebral disks show no special reaction. The crushed vertebra is converted into a yellowish-brown calcium containing fragment and disappears slowly due to the union of the other vertebræ, just as in certain cases of osteoporosis (Fig. 12). When the vertebra disappears the intervertebral disks unite. In all these changes of the osseous form the superficial areas and the periosteum remain intact and smooth. The cortical portions, no matter how thin, are never penetrated.

Even the microscopic pictures reveal striking peculiarities.

The elongation and spindle-shaped forms of the Gaucher cells, as found in the usual cases in the bone marrow, rise here to the highest potency. One finds spindle-shaped Gaucher cells in bundles which become interwoven in the greatest diversity (Fig. 13). In these situations the spindle cells are usually long and reveal sharp striations.

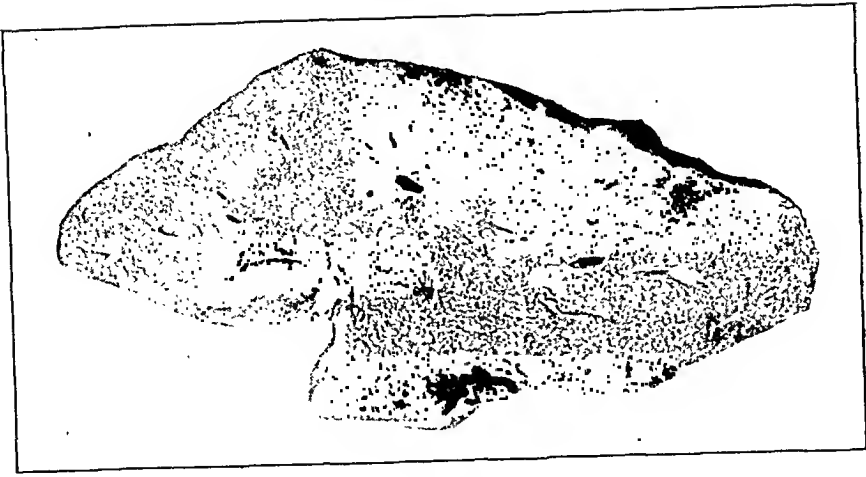


FIG. 1.



FIG. 3.



FIG. 4.

FIG. 1.—Liver in Gaucher's disease. Gray-white stippling in the parenchyma.

FIG. 2.—Section of Gaucher spleen. Nests of Gaucher cells.

FIG. 3.—Smear of material obtained on splenic puncture. Pappenheim stain. Multinucleated Gaucher cell. Cytoplasm wrinkled. There are no vacuoles.

FIG. 4.—Splenic tissue obtained by puncture in case of Gaucher's disease. Many Gaucher cells among pulp cells.

FIG. 5.—Nest of Gaucher cells with centrally located small artery.

FIG. 6.—Contents of one of the spaces of a cavernoma in a Gaucher spleen. Among the Gaucher cells are elements of myelopoiesis and several megakaryocytes.

FIG. 7.—“Cirrhosis” of the liver in Gaucher's disease.

FIG. 8.—The Gaucher substance. Kerasin crystals.

FIG. 9.—Dorsal half of left femur illustrating the skeletal form of Gaucher's disease. The marrow cavity is filled with nodules of Gaucher cells. Note atrophy of cortex and clublike swelling of the lower third.

FIG. 10.—Section through right tibia illustrating skeletal form of Gaucher's disease. The marrow cavity is diffusely filled with Gaucher cells. Rarefaction of the cortex.

FIG. 11.—Median section of the vertebral column of skeletal form of Gaucher's disease. Note destruction and collapse of 11th and 12th thoracic and 5th lumbar vertebrae. The intervertebral disks are not involved.

FIG. 12.—Median section of vertebral column in skeletal form of Gaucher's disease. Right half. Note destruction of 9th thoracic and 4th lumbar vertebrae. Gibbus. Intervertebral disks were not involved.

FIG. 13.—Microscopic section of Gaucher nodule from the marrow cavity of femur (see Fig. 9). Spindle-shaped Gaucher cells in bundles and interlacing in every direction. The fat cells in the bone marrow are preserved between them.

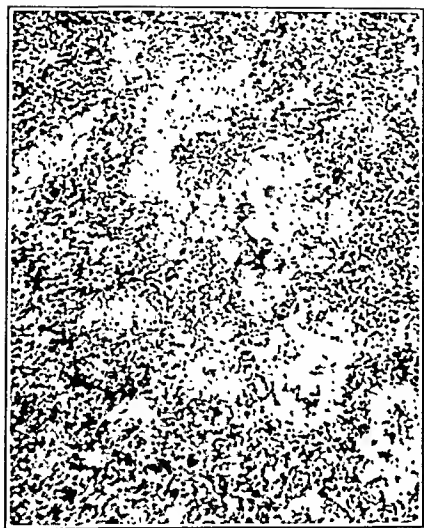


FIG. 2.



FIG. 6.

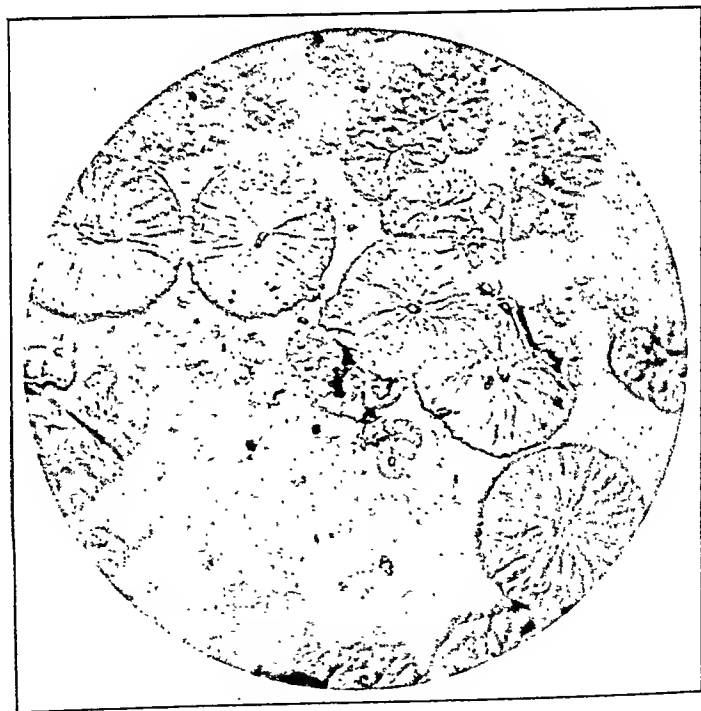


FIG. 8.



FIG. 5.

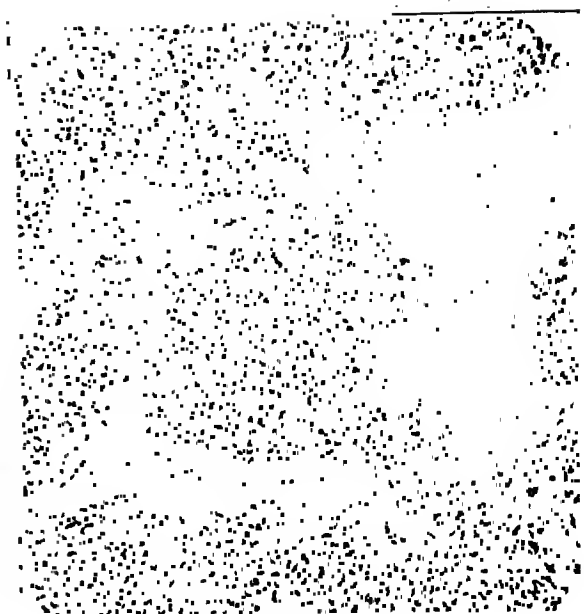


FIG. 7.

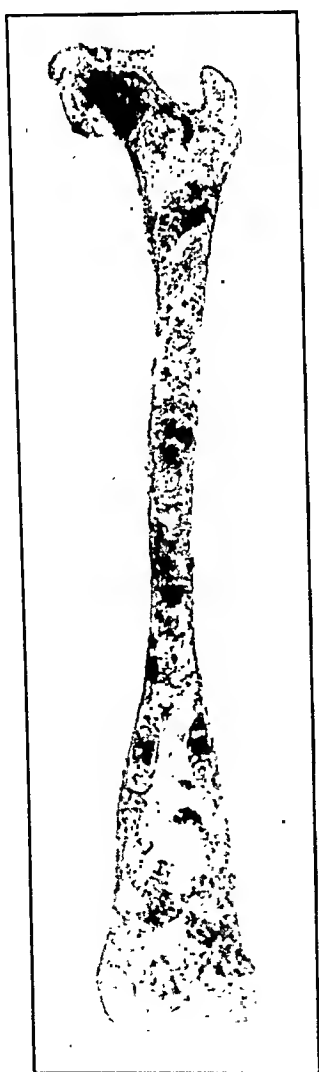


FIG. 9.

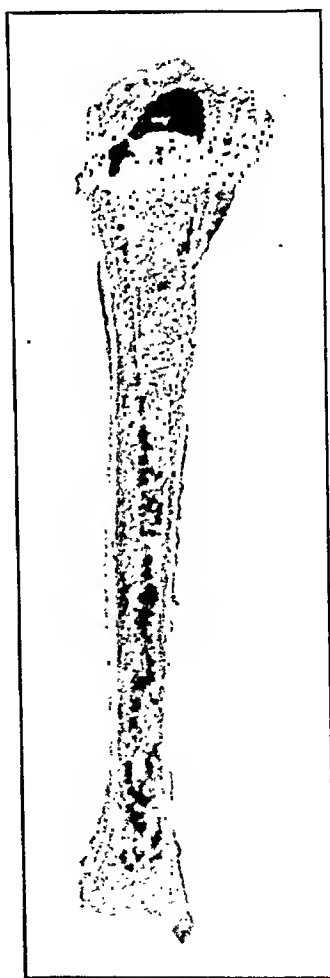


FIG. 10.

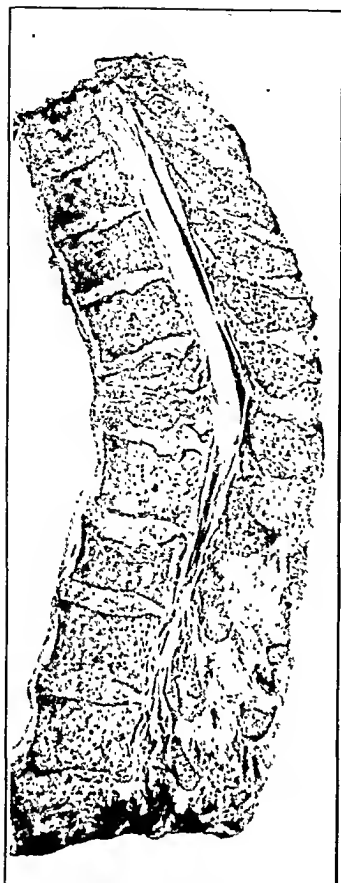


FIG. 11.

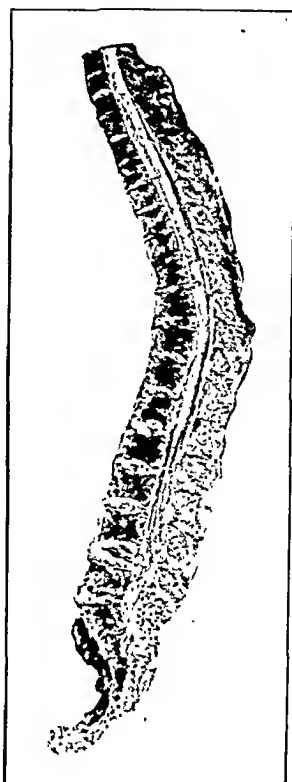


FIG. 12.



FIG. 13.

If it is considered *a priori* that the spindle shape of the Gaucher cells in the bone marrow is a result of compression, this fascicular type of growth contradicts this view. It represents a particular type of growth in itself. Microscopic examination confirms the observation that the cortex of the bone is never infiltrated by Gaucher cells even where it is thinnest. I have never found a single Gaucher cell in the periosteum nor on the surface of the bone, even in those cases in which the marrow cavities were completely filled. When finally the cortex, as, for example, in the case of the vertebrae, becomes completely atrophied by the expansive pressure of the Gaucher cell masses, the situation is entirely different. In this instance the masses of Gaucher cells lie free, so to speak, and further proliferation causes a bulging of the dura mater and a compression of the spinal cord.

One succeeds in making a correct clinical diagnosis of the nature of the bony disease in the osseous form of Gaucher's disease when the ordinary stigmata of the condition, for instance, the enlargement of the spleen and liver, pigmentation of the skin, pinguicula-like lesions of the conjunctiva and the hemorrhagic diathesis, are most evident. Moreover, this affection of the bones possesses a number of characteristic Roentgen pictures whose peculiar appearance may lead to a correct diagnosis.

On the Roentgen film the bones appear less opaque because of the generalized atrophy and deficiency of calcium. They are coarse-grained and worm-eaten because of the extreme porosity. The cancellous bone may show large defects, together with marked thinning of the cortex. In the shafts of the long bones there appear at times the outlines of large nodules within the medullary cavity. Collapse and deformity of the head of the femur are visible in the Roentgen film. In children the center of ossification of the head of the femur disappears when the flattening takes place. In the diffuse, as well as the more circumscribed widening of the medullary cavities of the long bones, the clublike swelling of the lower part of the femur often becomes evident. Especially noteworthy in diffuse involvement of the shafts of the long bones is the picture of an apparently reduplicated cortex, and in the vertebrae, compression of the lower dorsal or upper lumbar vertebrae. The intervertebral disks appear unchanged, whereas in tuberculous caries of the spine they are soon destroyed. Moreover, there are no reactive or regenerative changes in the bone and periosteum which are characteristic of Pott's disease and other diseases of the spine. Not only in the spinal column but also elsewhere, the Roentgen film shows the complete integrity of periosteum and the cartilage, even in severely involved portions of the skeleton. This certainly constitutes an abundance of roentgenologic evidence.

In some of the cases the skeletal changes became prominent after the spleen had been extirpated. It is conceivable that the removal

of the spleen which constitutes the main reservoir of the Gaucher substance is responsible for the involvement of the bones in such an intensive and extensive form. This hypothesis, however, is not absolutely necessary, for in such cases the liver and the lymph nodes might equally substitute for the spleen. However, the value of splenectomy as a therapeutic measure remains a problem.

VALUE OF SPLENECTOMY. Here opinions differ. In a recent compilation a not inconsiderable number of cases, 19.5 per cent, did not survive the splenectomy. It is admitted that in a number of the cases there is an improvement in the general nutrition and the condition of the blood and a disappearance of the hemorrhagic diathesis. On the other hand, it may be emphasized that in other cases the disease process itself progresses and that the involvement of the skeletal system, as I have stated, becomes evident only after the splenectomy. Since the spleen, in the course of Gaucher's disease, represents solely or almost entirely an organ depot, its extirpation can, in my opinion, have no influence on the process. There is, therefore, no rational indication for its removal. The symptomatic indication is another matter. In cases of especially severe anemia, hemorrhagic diathesis or where there is a particularly large organ, splenectomy may be indicated. However, the prognosis of the operation becomes worse in just these cases of severe anemia and copious hemorrhages, because of the poor general condition of the patient. Radiotherapy of the spleen has also been tried. The splenic enlargement may be diminished by this means but there is no noticeable influence upon the course of the disease.

ORIGIN OF THE GAUCHER CELL. The questions now remaining for discussion are the histogenesis and the pathogenesis of Gaucher's disease. What is the origin of the Gaucher cell? Does it arise from the endothelial cell or the reticulum cell?

In the spleen, for example, which has been the most important object of histologic study, do the nests of Gaucher cells arise from a proliferation of the endothelium of the walls of the sinuses? Is their alveolar form due to the shape of the sinus? Or are they of reticulum cell origin? Or is Gaucher's disease to be reckoned off-hand with the functional hyperplastic diseases of the reticulo-endothelial system, as Aschoff maintains? Is the controversy over this or that form of separation of types superfluous, considering that there is essential fundamental identity of endothelial and reticulum cells? Actually, a not inconsiderable number of authors have without undue consideration identified the histogenetic behavior of the reticuloendothelial storage cells in experimental storage of dyes, cholesterol, protein mixtures, etc., with the histogenesis of the lipid storing Gaucher cells.

There is, I believe, hardly a more striking example of the invalidity of the solution of morphologic problems by means of biologic functional induction. Especially in the case of the Gaucher spleen

there is morphologic proof, according to my observations, that the Gaucher cells arise from the reticulum cells—and only from these cells, and the endothelial cells remain completely uninvolved in the storage of Gaucher's substance. The very fact that in a considerable number of cases arterioles are found within a part of the Gaucher cell alveoli, shows that at least not all the Gaucher nests can arise from the endothelium of the venous sinuses. But the iron reaction of the splenic tissue makes it clear that the sinus endothelium is completely excluded as the maternal source of the Gaucher cells. If sections of the Gaucher spleen are treated with the Turnbull reagent, the pictures show most significantly that there is no Gaucher substance in the venous sinus endothelium, but, as a rule, only hemosiderin in considerable amounts; and conversely that the Gaucher cells which store the Gaucher substance contain either none or very irregularly distributed hemosiderin and purely in a facultative manner. This is an ever-recurring principle of the structure of the Gaucher spleen. On this account there occurs in Gaucher's disease an apparent and complete functional separation between endothelial and reticulum cells. Certainly in this instance, as in the diabetic xanthomatoses, the factor of time is of distinct significance. In animal storage experiments the organism becomes overloaded with relatively large amounts of storage substance in a short time, and because of this the entire storage system is activated. In Gaucher's disease the storage experiment of Nature extends over decades, and thus allows the especially differentiated tendency toward storage to proceed in its purest form. The reticulum cell origin of the Gaucher cell is also demonstrated in the lymph nodes and the bone marrow, while the endothelial origin remains unproven. However, by this observation alone, their origin is not settled. In the Gaucher cell nests of the spleen it can be shown with certainty that the Gaucher cells can arise from the adventitial and periadventitial cells, that is to say, the tissue histiocytes of the arterioles of the pulp. Thus in the liver the Gaucher cells arise from the connective tissue histiocytes of Glisson's capsule, the adventitia and periadventitia of the capsular vessels and the central veins. Therefore, Gaucher's disease is neither a "reticuloendothelial" disease, a disease of the entire "histiocytic apparatus" nor a histiocytomatosis, nor is it a pure reticulum cell disease. In addition to the reticulum cells of the spleen and the liver, the parent cell includes also the connective tissue cells of the bloodvessels of the adventitia and periadventitia and in addition the cells of Glisson's capsule. It is hence impossible to stigmatize Gaucher's disease with a mighty designation as a "reticuloendothelial disease."

PATHOGENESIS. Pathogenetically, Gaucher's disease exemplifies a primary congenital and familial metabolic disturbance on a constitutional basis. The metabolic disturbance is primary for all the

anatomic changes and clinical signs, just as the diabetic metabolic disturbance is for diabetic symptoms and visceral xanthomatoses, or the cholesterol feeding for cholesterol steatosis. The significance of the constitutional basis is indicated by the early onset, the familial occurrence, the predominance of the female sex and the susceptibility of the Jewish race. From several sources there has been assumed as the cause of the metabolic disturbance a primary disease hyperfunction of the reticuloendothelial system, because of the physiologic significance of the reticuloendothelial system as a metabolic apparatus. According to this viewpoint, it conditions at the same time the disturbance in metabolism and the storage of Gaucher substance. Proof for this viewpoint has not been presented. Every basis for it is lacking. One cannot even say whether the Gaucher substance is brought to the cells in finished form, or in the form of its building stones; whether "storage" corresponds to increased ingestion or diminished excretion, and whether the rich production of kersin signifies an increase or merely a disturbance of normal metabolism. When one speaks of "storage" in Gaucher's disease, he does it only in a designative sense, because of the obscurity of all these factors.

For the clarification of hemochromatosis in Gaucher's disease, one considers that there exists in lipid-storing cells of every sort the tendency to simultaneous storage of hemoglobinogenic pigments; also that with every added stimulation of the reticuloendothelial system there occurs an increased hemosiderosis, that is, an increased blood destruction. Therefore, in Gaucher's disease as well, the generalized lipoidosis is accompanied by an increased destruction of erythrocytes, that is, by hemochromatosis, for which, indeed, the persistent lipoidal overloading of the blood supplies a probable toxic cause. The facultative hemosiderosis of the Gaucher cells is only a special case of this general accompaniment of lipoidophagia.

The anemia of mild or severe intensity as well as the thrombopenia is based on the Gaucher cell infiltration of the bone marrow. The myelopoiesis in the Gaucher cell tissue, also in the cavernomas of the spleen, is compensatory; and, as I have already indicated, the thrombopenia is of significance for the hemorrhagic diathesis. Obviously these views on the pathogenesis of Gaucher's disease lie far within the realms of hypothesis.

A surer explanation of its developmental nature, I believe, can be offered on the basis of one fact, namely, the extraordinary constancy of the clinical, macroscopic, histologic, histogenetic, chemical and histochemical findings which are present in Gaucher's disease and which are not repeated in any other comparable pathologic process. This is evident in the enormous chronicity of the process which from the beginning develops into a pure morphologic and chemical tissue reaction, quite in contrast to the experimental lipoidophagia or the lipoidophagia of the spleen in diabetic xantho-

matosis, or above all, the disease which I shall discuss in my second lecture, the lipid splenohepatomegaly of the type of Niemann-Pick. The recognition of the latter disease as directly related to Gaucher's disease, but with, nevertheless, opposite essential disturbances of lipid metabolism, has excluded many difficulties in the clinical-anatomical definition of Gaucher's disease and has enabled me to define this disease as sharply as I have attempted to do today.

SPONTANEOUS SUBARACHNOID HEMORRHAGE.

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IN 1859, Samuel Wilks¹ wrote:

"Of all the difficult cases admitted into hospitals, those are the most perplexing where the patients are brought in in an insensible condition, and unable to give any account of themselves . . . and the surgeon has to choose between injury, poison, or disease, as a cause of his insensibility. . . . We refer in the present article especially to cases where an effusion of blood is found on the surface of the brain, without any apparent injury to the organ, and the question arises as to whether the cause be a blow, or arise from disease. . . . We therefore relate some cases where the effusion was spontaneous. . . ."

This introduction to Wilks' paper may serve equally well for a preface to the present one, in which is presented a series of 12 cases of spontaneous subarachnoid hemorrhage (hemorrhage into the subarachnoid space not caused by trauma) observed at the Baltimore City Hospitals in the last 3 years.

Previous Reports. Wilks¹ reported cases of spontaneous subarachnoid hemorrhage together with cases of traumatic origin. In 1912, Ehrenberg² reported 2 cases and reviewed 29 from the literature, for the first time describing spontaneous subarachnoid hemorrhage as a distinct clinical entity. Following that, the continental periodicals contained a number of case reports, but the malady was more or less overlooked in England and America. Leopold,³ in 1924, deplored this fact and reported 3 cases of his own. The stimulus of Symonds⁴ excellent paper, however, produced numerous case reports in the English-speaking journals; among which are those of Neal,⁵ Packard and Zabriskie,⁶ Richardson,⁷ Hall,⁸ and McIver and Wilson.⁹

Pathogenesis. Several conditions have been identified as causes of spontaneous subarachnoid hemorrhage and many others sus-

pected. The following list is offered in an attempt to classify the various etiologic factors:

I. BLOOD DYSCRASIAS.

II. EXTRINSIC DISEASES AFFECTING THE BLOODVESSELS OF THE SUBARACHNOID SPACE.

- (1) Meningococcus meningitis.
- (2) Tuberculous meningitis.
- (3) Meningovascular syphilis.
- (4) Embolism: (a) infected; (b) malignant.
- (5) Heat stroke.

III. INTRINSIC ABNORMALITIES OF THE BLOODVESSELS.

- (1) Thrombosis.
- (2) Degeneration of the bloodvessel wall: (a) arteriosclerotic; (b) hypertensive; (c) in acute infections (as typhoid fever); (d) from poisoning (as alcohol)(?).
- (3) Congenital nevi.
- (4) Congenital aneurysms.

I. Cases of subarachnoid hemorrhage have occurred in various blood dyscrasias, as pernicious anemia,¹⁰ sickle-cell anemia,¹¹ hemophilia and leukemia. The infrequency of reported cases is probably due to the fact that subarachnoid hemorrhage is often overlooked in the presence of the predominating disease. The present series contains no cases of this kind.

II. Pyogenic and tuberculous conditions in the meninges may cause necrosis of vessel walls with resulting hemorrhage, but actually this rarely occurs, because in tuberculous meningitis there is eccentric thickening of the adventitia and obliterative thickening of the intima—conditions which are not likely to result in rupture—while in meningococcic meningitis there is infiltration of polymorphonuclear leukocytes around the vessels, but little involvement of the vessel wall. There are no cases in the present series.

With respect to meningovascular syphilis, Turnbull¹² says that the usual lesion in smaller arteries is an obliterative endarteritis with thrombosis. In some cases, however, in which the adventitia and media become weakened before the intima has thickened, he states that rupture may occur.

Sands¹³ recently reported 2 cases and stated that, while syphilitic meningitis as a cause of subarachnoid hemorrhage is rare, it does occur, and may be overlooked.

In 4 cases (3, 5, 7, 10) in the present series, there was a positive blood Wassermann reaction, and in Cases 3 and 7 positive reactions on the cerebrospinal fluid as well. Meningovascular syphilis may be considered as a likely etiologic factor in these instances. This proportion of cases associated with syphilis (33 per cent) is high as compared with Symonds'⁴ report of less than 10 per cent, but the former figure is not surprising in a hospital in which 7.5 per cent of the patients have a positive Wassermann reaction.

Emboli of various kinds may initiate rupture and hemorrhage, but this is usually an insignificant part of the larger disease.

Cases of subarachnoid hemorrhage have been reported as due to heat stroke. McKenzie and LeCount¹⁴ found minute hemorrhages in the leptomeninges in 2 out of 37 autopsies performed upon patients dying from heat stroke. In these cases the cerebrospinal fluid was clear and colorless, but it can be assumed that in some instances these hemorrhages might be sufficient to cause yellow coloration of the fluid. In Case 1, the patient became unconscious while working in the sun on a very hot morning. Heat stroke may have been the causative factor.

III. The largest class is that in which there is some abnormality of the vessel itself. Leadingham¹⁵ reported a case of sinus thrombosis causing hemorrhage into the subarachnoid space.

In a number of instances there is present hypertension or arteriosclerosis, or both. In 5 cases (2, 7, 8, 9 and 11) in the present series of 12, the blood pressure was considerably above normal and remained elevated during convalescence. In Case 7, syphilis is a factor to be considered in addition to hypertension.

Subarachnoid hemorrhage associated with nevi has been reported by Cushing.¹⁶

Considerable data and not a few theories have accumulated upon the subject of aneurysm of the intracranial vessels. The articles by Fearnside¹⁷ reporting 44 cases, and by Wichern¹⁸ reporting 21 cases, are the first comprehensive reviews.

Of the later papers, those by Parker¹⁹ and Forbus²⁰ are distinct contributions. The former attempts to correlate autopsy and clinical findings, and shows that there is a difference in the clinical picture between rupture of the anterior arteries of the circle of Willis and their branches, and rupture of the posterior group.

Forbus found muscular defects in the media of cerebral arteries in cases of aneurysm and in some cases in which no aneurysms were found. These defects he traced to defective embryonic development. He believes that the repeated pounding of the blood column against these weak points will cause aneurysms, which eventually may rupture.

In the present series Case 5 was found at autopsy to have a ruptured aneurysm of the right anterior cerebral artery. Cases 4 and 12 may have been due to ruptured aneurysm, but the presumption is made by elimination, since the patients showed no evidences of syphilis, arteriosclerosis, hypertension or acute infectious disease.

Analysis of Symptoms. The onset was sudden in 7 cases, slow in 4, and in 1 instance was unknown. In the 11 in which the onset was known, it occurred with a sudden loss of consciousness in 6, once accompanied by delirium and once by delirium and convulsions. In the remaining 5, headache was the first symptom.

The various symptoms present in the 12 cases reported are listed

in Table 1, according to the frequency of their occurrence. Headache, while present as the initial symptom in 5 cases, was complained of at some time during the course of the illness by 9 patients. The syndrome began with unconsciousness in 6 cases and unconsciousness came on later in a 7th case. Three of the patients, after recovering consciousness, remained dull, sleepy and apathetic for a variable period, ranging from a few hours to 2 weeks in duration. Headache was accompanied by pain and stiffness of the neck in 3 cases. Vomiting and delirium were each present in 2 cases, and the other symptoms enumerated in Table 1 in 1 case each.

TABLE 1.—SYMPTOMS PRESENT IN 12 CASES OF SPONTANEOUS SUBARACHNOID HEMORRHAGE.

	No. of cases.	Percentage of total cases.
Headache	9	75
Unconsciousness	7	58
Dullness and sleepiness	3	25
Pain and stiffness of neck	3	25
Vomiting	2	17
Delirium	2	17
Paresthesias of scalp	1	8
Soreness along spine	1	8
Specks before eyes	1	8
Diplopia	1	8
Transient hemiparesis	1	8
Stiffness of legs	1	8

TABLE 2.—SIGNS PRESENT IN 12 CASES OF SPONTANEOUS SUBARACHNOID HEMORRHAGE.

	No. of cases.	Percentage of total cases.
Hyperactive deep reflexes	5	42
Choked disks	4	33
Unequal pupils	4	33
Hypoactive deep reflexes	3	25
Absent abdominal reflexes	3	25
Positive Kernig's sign	2	17
Positive Babinski's sign (or equivalent)	2	17
Nystagmus	2	17
Pulse-rate below 50 per minute	2	17
Seventh nerve paresis	2	17
Twelfth nerve paresis	1	8
Strabismus	1	8
Positive Brudzinski's sign	1	8
Absent deep reflexes	1	8
Leukocyte count above 10,000 per c.mm.	5	42
Temperature above 100° F.	5	42

Analysis of Signs. As shown in Table 2, the tendon reflexes were the most variable signs. Hyperreflexia was present in 5 cases, hyporeflexia in 3, and absence of deep reflexes in 1. Papilledema was found in 4 cases, unequal pupils in 4, nystagmus in 2 and strabismus in 1. Transient weakness of the facial nerve occurred in 2 patients, and of the hypoglossal in 1. Other abnormal signs were: absent abdominal reflexes, 3 cases; positive Babinski

sign or its equivalent, 2 cases, and positive Brudzinski sign, 1 case. All the abnormal signs cleared up during the patients' stay in the hospital, except in the 2 instances where death intervened.

Leukocytosis and moderate increase in temperature for the few days following the hemorrhage have been noted as occurring rather frequently. As will be seen in Table 2, each occurred in nearly half of the present series. The highest leukocyte count was 23,800 per c.mm. in Case 11.

Diagnosis. The usual clinical picture of subarachnoid hemorrhage is the sudden onset of unconsciousness, usually preceded by headache. Unconsciousness may last for a few minutes or several days and may be followed by dullness and drowsiness, by convulsions and delirium, or merely by a slight headache, which soon wears off and leaves the patient feeling perfectly well. The importance of headache as a suggestive symptom of hemorrhage into the meninges is well shown in Table 1, especially if accompanied by pain and stiffness in the neck.

Meningeal irritation or direct pressure effects are responsible for the signs. The deep reflexes may be hyperactive, normally active, diminished or absent. Superficial reflexes may be absent and various pathologic signs may be found, especially the Babinski sign. Papilledema, either unilateral or bilateral, and slowing of the pulse rate are the most suggestive signs of increased intracranial pressure.

Remembering that subarachnoid hemorrhage is more often overlooked than erroneously diagnosed, the important feature in the diagnosis is to suspect its presence and perform a spinal puncture in every case of coma, unless some other causative factor is certain. The present series of cases would suggest also that in instances of headache unexplainable on any other basis, consideration of subarachnoid hemorrhage and consequent spinal puncture are warranted.

If the spinal fluid contains blood there are only a few conditions to be ruled out. Traumatic blood introduced at the time of puncture is differentiated in three ways from bloody spinal fluid caused by hemorrhage into the subarachnoid space:

1. In the traumatic puncture the blood is not evenly mixed with the cerebrospinal fluid, but will color the first of 3 successive tubes darker than the third; in subarachnoid hemorrhage all the tubes will be colored alike.

2. The former will clot (if there is a sufficient amount of blood); the latter will not.

3. If the bloody fluid in subarachnoid hemorrhage be centrifugalized immediately, or allowed to stand, the supernatant fluid will be xanthochromic.

If the puncture is not done until several days after the onset the fluid may no longer be bloody, but merely xanthochromic.

In addition to subarachnoid hemorrhage, bloody or xanthochromic

fluid may occur in intraventricular hemorrhage, in cerebral hemorrhage with rupture into the ventricles or into the subarachnoid space, and in traumatic meningeal hemorrhage.

Patients with intraventricular hemorrhage show profound prostration and rarely recover. If they do not die they usually show residual paralyses. Hemorrhage into the substance of the cerebrum will show more lasting effects than subarachnoid hemorrhage, and often leave permanent paralyses.

Traumatic hemorrhage is often hard to differentiate, even at autopsy. Munck,²¹ in analysis of 9 debatable cases, gives useful pointers for making the distinction. If there is fracture of any bone of the skull, if there are signs of trauma on the scalp, or if the hemorrhage is found at necropsy to be confined to a small area over which injury is known to have occurred, the case may be considered traumatic. In the absence of sufficient trauma, especially if there is demonstrable disease of the bloodvessels, the hemorrhage is classed as spontaneous.

Treatment. The relief of intracranial pressure is the end sought for; whether by repeated spinal drainages, intravenous hypertonic glucose solutions, or frequent doses of magnesium sulphate by mouth.

At the present time the accepted procedure at the Baltimore City Hospitals is to perform one puncture for diagnostic purposes and no more for 1 week (unless marked pressure symptoms require it). This time is allowed for the bleeding vessel to attain some degree of repair. After this the patient is given a puncture every 3 days (or oftener, in the presence of markedly increased intracranial pressure) until the fluid is colorless and the abnormal signs and symptoms have all disappeared. Intravenous glucose and drastic purgation are reserved for cases in which spinal drainage alone fails to give relief.

Case Reports. CASE 1 (Med. No. 17516).—J. S., a colored male, aged 41 years, fell unconscious while at work on a hot summer morning. He roused from coma after 3 hours, but was alternately stuporous and raving on admission to the hospital.

The relevant findings on examination were: pulse, 120; moderate neck rigidity; irregular pupils with the right larger; slight sclerosis of retinal vessels; slight left facial weakness; normally active deep reflexes; moderate sclerosis of peripheral vessels; blood pressure, 110 systolic, 80 diastolic.

Urinalysis: albumin ++; many white cells (negative after 2d day). The leukocytes were 11,200 per c.mm. The spinal fluid was bloody and became xanthochromic on subsequent taps. Blood and spinal fluid Wassermann reactions were negative.

Gradual but complete recovery took place, with eventual return of the spinal fluid to normal. The patient was discharged, fully well, after 6 weeks.

CASE 2 (Med. No. 17589).—M. E. L., a white female, aged 50 years, after a sudden attack of unconsciousness with right hemiplegia, remained comatose for 31 hours and was apathetic for the next 2 weeks.

Hemiplegia had disappeared by the 13th day, when the patient entered the hospital. Examination showed: temperature, 100.4° F.; pulse, 104;

tenderness of lumbar spine; blood pressure 196 systolic, 114 diastolic; sclerotic peripheral vessels; hyperactive deep reflexes suggestive right Babinski and Oppenheim.

Urinalysis: few red and white cells; trace of albumin; occasional granular cast. The blood count was within normal limits. The spinal fluid was xanthochromic after a small amount of old blood had settled out. Blood and spinal fluid Wassermann reactions were negative.

Recovery was complete and the patient was discharged in 3 weeks.

CASE 3 (Med. No. 18255).—H. S., a white male, aged 33 years, had severe pain in the left temple, plus sensations of "pins and needles" and heat and cold for 2 weeks, followed by sudden onset of delirium, convulsions and coma.

There was history of previous antiluetic treatment.

Examination showed: coma, alternating with delirium and convulsions; temperature, 99.4° F.; pulse, 128; blood pressure, 90 systolic, 60 diastolic; bilateral choked disk; slight ptosis of left eyelid; left facial weakness; protrusion of tongue to the left; rigidity of the neck; hyperactive patellar reflexes; positive Kernig; positive left Oppenheim and suggestive left Babinski. The pupils reacted to light and in accommodation, the right being larger.

The leukocytes were 15,200 per c.mm. Roentgen ray revealed no fracture of the skull. The spinal fluid was bloody (becoming xanthochromic on later taps). Wassermann reactions on blood and spinal fluid were 4+.

Gradual improvement occurred under antiluetic therapy and occasional spinal punctures. The patient was discharged completely well 15 weeks after admission.

CASE 4 (Med. No. 18306).—W. L., a white male, aged 41 years, after a 3-day alcoholic debauch fell unconscious when he attempted to get out of bed. Delirium alternated with coma the remainder of the day, and he was brought to the hospital that night, where examination showed the following relevant facts: temperature, 102° F. (rectal); pulse, 72; left pupil larger; no reactions of pupils to light; hyperactive deep reflexes; absent abdominal and cremasteric reflexes; bilateral Babinski.

The leukocytes were 15,400 per c.mm. The spinal fluid was bloody and became xanthochromic on later taps. Wassermann reactions on blood and spinal fluid were negative.

The pupils regained their normal reaction to light within the first week, and during the same time the deep reflexes on the right returned to a normal status, followed 2 weeks later by those on the left. Delirium was controlled by spinal punctures during the first 2 days, and was followed after that time by mental sluggishness which cleared up very slowly. The mental condition had just about reached normal when he was discharged at his family's request 6 weeks after admission.

CASE 5 (Med. No. 14413).—S. H., a colored male, aged 33 years, fell unconscious at work. Coma, lasting a few minutes, was followed by several hours of mental dullness. Then coma returned, with convulsions.

Examination showed: pulse, 120; blood pressure, 230 systolic, 90 diastolic; bilateral choked disk; deep reflexes absent.

The spinal fluid was bloody on the day of onset and xanthochromic 2 days later.

Convulsions became less frequent as the patient became weaker. The patient died 2 days after admission.

Postmortem examination (Forbus²⁰ Case 7) showed diffuse hemorrhage over the surface of the brain, particularly at the base, and a ruptured aneurysm of the right anterior cerebral artery. The aneurysm showed no evidence of syphilis.

CASE 6 (Med. No. 17409).—J. P., a colored male, aged 42 years, had a left temporal headache 1 week before he suddenly lost consciousness while urinating. Coma lasted 1 hour and was followed by headache and diplopia. The patient had received an incomplete course of antiluetic treatment in the past.

Examination showed: temperature, 100; blood pressure, 120 systolic, 80 diastolic; enlarged epitrochlear nodes; left internal strabismus; left horizontal nystagmus; hypoactive deep reflexes.

Leukocytes were 11,100 per c.mm. The spinal fluid was xanthochromic. The spinal fluid Wassermann was negative, but the blood Wassermann was 4+.

The patient improved rapidly with spinal drainages and antiluetic treatment. Headache, strabismus and nystagmus disappeared and the patient was discharged 2 weeks after admission.

CASE 7 (Med. No. 17571).—E. N., a colored male, aged 42 years, had an attack of unconsciousness while in church, lasting for a few minutes and followed by sleepiness and headache.

Examination on entrance to the hospital 4 days later showed: pulse, 48; blood pressure, 240 systolic, 120 diastolic; deep reflexes hypoactive; otherwise negative, except for mental sluggishness.

Urinalysis showed: albumin +++; many white cells, hyalin and granular casts. There was moderate impairment of renal function as judged by the Mosenthal test. Blood counts were within normal limits. The spinal fluid was bloody, becoming xanthochromic on later taps.

Gradual improvement occurred. The pulse rate became normal, but the blood pressure remained elevated. The patient was fully recovered when he was discharged 6 weeks after admission.

CASE 8 (Med. No. 17820).—F. H., a colored male, aged 34 years, was found 2 days after disappearing from home. He was mentally confused and remembered nothing of the period of his absence.

Examination showed marked mental confusion and inability to answer even the simplest questions. The blood pressure was 245 systolic and 150 diastolic, and the examination was otherwise negative.

The spinal fluid was xanthochromic after old blood had settled out. Wassermann reactions on blood and spinal fluid were negative.

The urine contained a faint trace of albumin and an occasional hyalin cast for the first week and was negative thereafter. The nonprotein nitrogen was 62 on admission, gradually dropping to normal in 2 weeks.

The deep reflexes changed from a state of hyperactivity to hypoactivity and then became normal 2 weeks after admission. Mental confusion and dullness left very slowly. At the time of discharge, 9 weeks after admission, normal mental status had returned, but the patient was never able to recall the incidents of his 2 days' disappearance.

CASE 9 (Med. No. 14866).—H. W., a colored male, aged 35 years, had a frontal headache for a week which disappeared and returned in severer form 5 days later, causing him to seek hospitalization.

On examination he was found to have a temperature of 100° F. by rectum; pulse, 46; bilateral choked disks; slight ptosis and facial weakness on the right; biceps and triceps diminished; knee-jerks normal; peripheral vessels slightly thickened; blood pressure, 160 systolic and 100 diastolic.

Urinalysis: faint trace of albumin and occasional hyalin and cellular cast. Roentgen ray showed no skull fracture; ventriculogram revealed no evidence of brain tumor.

The spinal fluid was blood tinged and later became xanthochromic. Blood and spinal fluid Wassermann reactions were negative.

Two weeks after admission the pulse rate had increased to 76, the blood pressure was 140 systolic and 80 diastolic, and the abnormal neurologic

signs had disappeared. The patient was symptom-free and remained so until discharge, 5 weeks after admission.

CASE 10 (Med. No. 15367).—G. C., a colored female, developed headache; 4 days later, nausea and vomiting; and 6 days later, pain and stiffness of the neck.

Examination 9 days after the onset revealed stupor; blood pressure, 130 systolic and 96 diastolic; dilated, irregular pupils, the right being larger, reacting to light and on accommodation; painful, stiff neck; absent abdominals, normally active tendon reflexes.

Spinal fluid was bloody and, on later taps, xanthochromic. The blood Wassermann was 4+; the spinal fluid Wassermann, negative.

Improvement began on the 4th day after admission; abnormal symptoms and signs were gone in 2 weeks; and the patient was discharged perfectly well 3 weeks after admission.

CASE 11 (Med. No. 17199).—E. L., a colored female, aged 59 years, while hanging clothes on a line was seized with severe, lancinating pain in the back of the neck, accompanied later by vomiting, bitemporal headache and soreness in the lumbar region. When no improvement occurred after 2 weeks she entered the hospital.

Examination showed: temperature, 101.4° F.; pulse, 75; sclerosis of retinal vessels; moderately enlarged heart with systolic murmur at apex, transmitted over the precordium; tortuous, sclerotic peripheral vessels; blood pressure, 210 systolic, 120 diastolic; hyperextension and stiffness of neck; tenderness along spine; positive Kernig; adductor spasm of thighs; hypoactive deep reflexes.

Leukocytes were 23,800. The spinal fluid was bloody on admission and xanthochromic 5 days later.

Headaches ceased in a few days and the patient improved in other respects, until one day, about a month after the onset, she suddenly fell back unconscious. Coma lasted a few hours and was followed by bitemporal headache. Spinal fluid was again bloody and the leukocytes rose to 16,700 (having previously dropped to normal limits) on the 4th day after this second attack.

Gradual improvement began again and the patient was practically well, when she developed bronchopneumonia and died, 1 month after the second attack. Autopsy was refused.

CASE 12 (Med. No. 18290).—V. D., a white male, aged 41 years, developed severe throbbing headache, which subsided after taking capsules prescribed by a physician. The next afternoon, however, the patient's legs became gradually so stiff that he could not walk. There was no pain or swelling of the legs.

Examination showed an alert and coöperative patient; temperature, 99.6° F.; pulse, 80; blood pressure, 110 systolic, 70 diastolic; bilateral choked disk; positive Brudzinski; moderate stiffness of the neck; positive Kernig; hyperactive deep reflexes; no redness, heat, swelling or tenderness of the lower extremities.

Blood counts and urinalyses were within normal limits. The spinal fluid was xanthochromic. Blood and spinal fluid Wassermann reactions were negative.

The patient recovered rapidly so that he was free from signs and symptoms after 1 week and insisted on going home after 2 weeks.

Conclusions. The salient points revealed by this study of a small group of cases of subarachnoid hemorrhage are:

1. A variety of pathologic conditions may cause hemorrhage into the subarachnoid space.

2. The syndrome may present a wide variety of symptoms and signs.

3. In every case of coma of unknown origin, a diagnostic spinal puncture is imperative.

4. Headache is a prominent and sometimes the only symptom. A diagnostic spinal puncture is justified, therefore, in any case of unexplained headache.

NOTE.—The writer wishes to thank Dr. Thomas R. Boggs for permission to present these cases, and Dr. Boggs and Dr. Paul Padgett for their advice and helpful suggestions.

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THE USE OF VARIOUS GASES IN ENCEPHALOGRAPHY.

A SUMMARY OF 210 CASES, USING THE SIMULTANEOUS DISPLACEMENT APPARATUS.*

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Most workers in the field of encephalography have felt that the radiographic method of investigating the ventricular and subarachnoid systems after replacement of the cerebrospinal fluid with air would find much more extensive use in the study of the minor as well as the graver lesions of brain and meninges if the procedure could be made safer and less discomforting to the patient. For the past 11 years it has been the author's aim to obviate these two main

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deterrents to the more universal application of the encephalographic method. The present paper deals with the efforts in that direction, which have permitted the successful encephalography of 210 patients without fatality or serious accident.

TABLE 1.—CLASSIFICATION OF CASES.

TABLE I.—CLASSIFICATION OF CASES.			Cases.
A.—According to gases used.			
Air		Unfiltered	40
Air		Filtered	115
Carbon dioxid		Filtered	3
Nitrogen from	$\left\{ \begin{array}{l} \text{NH}_4\text{NO}_2 \text{ (15)} \\ \text{NH}_4\text{Cl} + \text{NaNO}_2 \text{ (23)} \\ \text{Commercial tank (2)} \end{array} \right\}$	Filtered	40
Helium from	Commereial tank		12
B.—According to Clinical Diagnosis.			
No gross organie abnormality (psychosis, psychoncurosis, psychoasthenia)			57
Cerebrospinal lues			65
Vaseular disease of unknown origin			16
Posttraumatic headaehe			15
Petit or grand mal			12
Encephalitis			9
Apoplectie hemiplegia			3
Obliterative subaraehnoiditis			3
Congenital hydrocephalus			2
Brain tumors (not posterior fossa)			10
Posterior fossa tumors*			8
Cord tumors or adhesions*			10

* The relatively large number of cases of posterior fossa and cord tumors is due to the kind courtesy of Dr. E. J. J. King of Bellevue and Misericordia, Dr. R. A. Gerber of Harlem, and Dr. I. J. Sands of the Brooklyn Jewish, who felt that the use of the apparatus makes for added safety, and thus invited me to do some of their more difficult tumor cases at the respective hospitals.

Even as early as 1921 it was felt that the chief element of danger in the withdrawal of any appreciable amount of spinal fluid is the sudden alteration in the intracranial pressure. The danger appears to vary with the amount of fluid withdrawn before its equivalent in air is injected, being grave where the replacement unit is 20 cc., and much less serious where only 5 cc. is withdrawn at a time. The knowledge that the smaller the replacement unit the less the disturbance to the intracranial pressure prompted the development of an apparatus for the simultaneous (drop by drop) displacement of fluids by air or some other gas.^{1,2}

The principle of the apparatus is that "fluid will seek its level," so that if the air to be injected is placed in a cylinder at a lower level than the spine, the inlet and outlet being connected with the subarachnoid spaces by lumbar puncture, making a continuous closed system, the cerebrospinal fluid will descend by gravity into the cylinder, and as it does so, an equivalent quantity of gas is forced out of the cylinder up into the subarachnoid spaces.

In the first 4 cases the spine was punctured in 2 interspaces, according to the method developed by Bingel;³ the fluid inlet tube

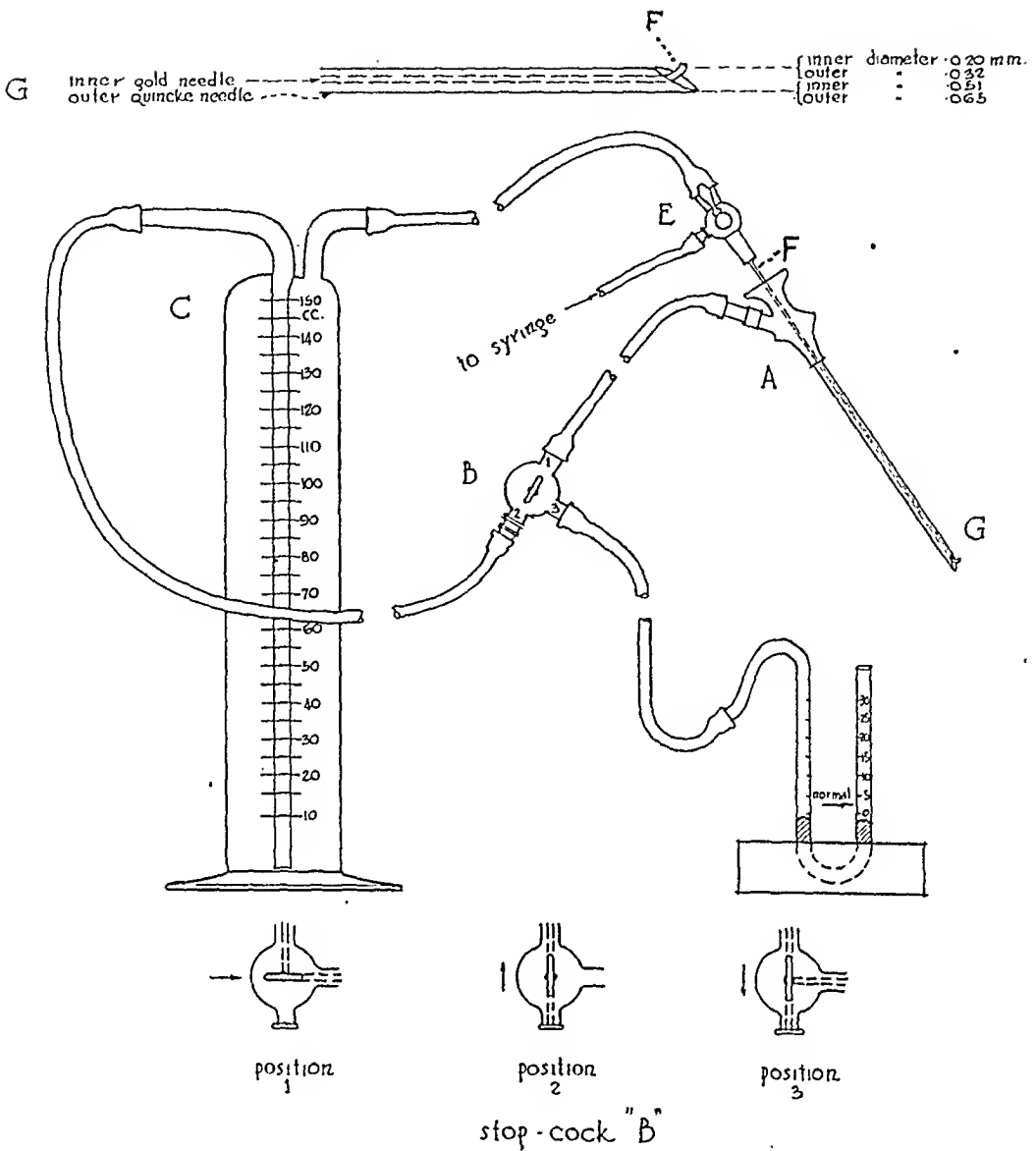
of the simultaneous displacement apparatus being connected to the lower puncture needle and the gas-conveying tube to the interspace above. To obviate the discomfort of the double spinal puncture a fine cannula was substituted for one of the needles and made to fit inside the other one, forming a "needle within a needle" unit that requires only a single lumbar puncture (Fig. 1). As such the apparatus was used in the succeeding 206 cases.

The writer admits that the use of the simultaneous displacement apparatus makes this method of encephalography manifestly less simple than the one generally employed now, the syringe and 2-way stopcock, where 5 cc. of fluid is withdrawn and an equivalent amount of air injected at a time. The factor of *added safety*, however, justifies its use in the mind of the author. The general mortality of encephalography is still quoted at 2 per cent,⁴ while by use of the simultaneous displacement apparatus the author has not had a single fatality in the 210 cases, 8 of which were posterior fossa tumors.

The second difficulty with encephalography, the reaction, consists of severe headache that occurs in almost every case. Occasionally shock supervenes, with its usual symptoms: vomiting, cold sweat, weak and thready pulse, and fall of blood pressure. The shock reaction in this series of 210 cases occurred infrequently and was at no time so severe as to require any treatment; the fall of blood pressure never being above 20 mm. of mercury.

The headache, however, is almost constant and baffles all attempts at circumvention. It is severe for 5 to 6 hours, and commonly lasts 1 to 4 days. It appears after the introduction of about 30 cc. of air and indicates absence of obstruction in the spinal canal, as well as the presence of the gas in the subarachnoid spaces over the brain, especially the frontal lobes. Sedative, such as chloral and luminal, and opiates such as morphin $\frac{1}{8}$ gr. in combination with hyoscin $\frac{1}{15}$ gr. are thus far the most promising methods of treatment for the headache.

It was thought at first that particulate matter in the injected air, such as dust, was responsible in part for the severe reaction. Therefore, in 115 cases the air was filtered through a water column before injection (Fig. 2). The headache during injection was the same as in the unfiltered cases, yet there seemed to be less severe reaction *after* the procedure than in the first 40 unfiltered control cases. At no time did we feel compelled to tap the spine for the relief of the post-injection symptoms. Nevertheless, for purely scientific purposes, spinal taps were performed 1 to 3 days after the injection of filtered air in 6 cases. The cell count was uniformly the same or even less than at the time of injection. This is to be contrasted with the pleocytosis that occurs after the use of ordinary injection methods.⁵ It would appear then that filtration of the gas used in encephalography, although not of striking value in obviating the headache



SIMULTANEOUS · DISPLACEMENT · APPARATUS ·

FIG. 1.—THE SIMULTANEOUS DISPLACEMENT APPARATUS. The apparatus consists of a cylinder (C), with an inlet tube reaching to its bottom and connected to a spinal needle (A), and an outlet tube leading from the cylinder top to a fine cannula (F) made to fit inside the first needle. A mercury manometer is placed as a side-arm to the 3-way stopcock at B to measure the intraspinal pressure. The cylinder is kept at a lower level than the spine; the lumbar puncture is made; and the fine cannula is inserted snugly into the larger needle, the system thus becoming a closed one. As the cerebrospinal fluid descends through the large needle to the bottom of the cylinder it forces an equivalent amount of gas which it displaces from the cylinder up into the small cannula and the subarachnoid spaces. The speed of exchange of gas for fluid is controlled by raising or lowering the cylinder. The 3-way stopcock at B serves for pressure readings when turned to position 3, and for the usual working of the apparatus in position 2. Stopcock E is used to clear the air cannula in case fluid filled it, drawing up some gas from the cylinder (stopcock in position 1), changing to position 3 and injecting it into the spinal canal, then returning to position 2 for the usual exchange of gas and fluid. The detailed description of the apparatus and its workings can be found in the original article describing it (*quod ride*).

and other reactions, is to be recommended on the score of diminishing postoperative reactions, such as meningeal reaction and pleocytosis.

Another attempt at obviating the postinjection reaction was made about 5 years ago by the author, who felt that the reaction may be due not only to the mechanicophysical properties of the gas, such as its expansibility and solubility, but also to its chemical properties. This prompted the substitution of different gases for air in encephalography.

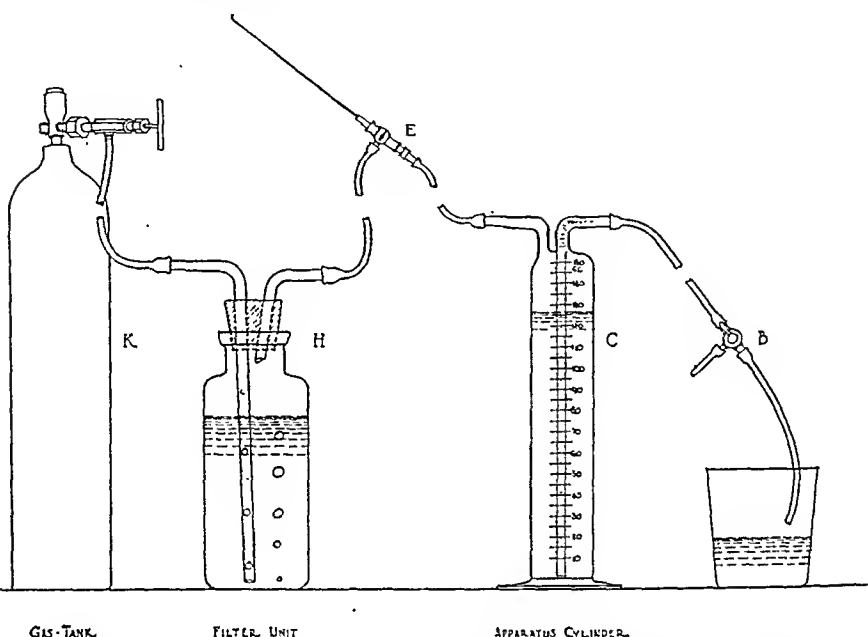


FIG. 2.—METHOD OF FILTERING THE GASES USED. The cylinder (*C*) and the accompanying tubing and stopcocks are filled with water and heated in the sterilizer for 20 minutes. The gas to be introduced (*K*) is filtered through a column of sterilized water (*H*), and is then allowed to displace the fluid in the cylinder, leaving about 0.5 cc. to act as a seal for the fluid-carrying stopcock, and as a gravity starter when the exchange of fluid and gas commences. The stopcocks are closed, separated from the filtering unit, and the apparatus is now ready for the replacement of the cerebrospinal fluid by the filtered gas contained in its sterilized cylinder.

When air is the gas used, the arrangement is exactly the same except that the tank is not present. The cylinder (*C*) which was previously filled with water and sterilized, is raised high, making the fluid in it flow out into the cup. This draws the air through the filtering unit (*H*) into the cylinder. The stopcocks are now closed, separated from the filtering unit, and the apparatus is ready for use.

In the first 3 cases carbon dioxide was tried. Because of its great solubility in spinal fluid, air had to be mixed with it. The calculation of the relative amounts of air and carbon dioxide necessary to maintain proper pressure relations after withdrawing the spinal fluid was so difficult as to make the method impossible. The reactions were severe and served to emphasize the necessity of using insoluble gases to replace the spinal fluid.

Nitrogen was then employed in 40 cases with more promising results. The gas was obtained by heating a small flask containing 5 gm. of ammonium chlorid, 5 gm. of sodium nitrite and about 20 cc. of water. The gases generated were led through a column of water, which acted as a filter, absorbing the ammonia that comes off in appreciable quantities, especially at the beginning of the heating. The filtered nitrogen was finally allowed to displace the water in the apparatus cylinder. (The nitrogen also can be prepared by heating an ammonium nitrite solution, or from a commercial nitrogen tank). Whichever way the nitrogen was prepared, the headache was found in almost all cases to be less severe than with air. The difference between nitrogen and air, however, cannot truthfully be said to be very striking.

Not satisfied with nitrogen, the author turned in the last 12 cases to the even more inert gas, helium, obtaining it, in pure state, at considerable expense from commercial cylinders. The helium was filtered through water in the same manner as the nitrogen. The headache in these 12 helium cases have been almost uniformly less severe than with the other gases. Although nothing definite can be said about helium as yet, the results are encouraging enough to suggest its continued trial use in the future.

It should be emphasized that the simultaneous displacement apparatus lends itself so easily to filling cavities by different gases that it served as the starting point and nucleus for the project of substituting different gases for air in encephalography. This reverts back to the original aim to make the apparatus a safe means of replacing the liquid in any closed body cavity by any other gas, or the gas in a cavity by any other liquid, either for diagnostic or therapeutic purposes. The apparatus not only enables one to drain off all the cerebrospinal fluid possible by substituting some gas for it, but permits the reverse procedure, the replacement of the gas injected into the canal by the patient's own cerebrospinal fluid, or any other fluid the therapist may desire, such as saline, serum, or medicated spinal fluid. It was the intention of the writer in 1924 to make use of this form of complete spinal drainage with gas replacement of the spinal fluid and redisplacement by medicated fluid or serum in cases of meningitis, following along the work of Sharp,⁶ and in cases of cerebrospinal lues according to the work of Dercum⁷.

In conclusion it may be said that whereas the question of safety in encephalography has been dealt with and met in great part by the simultaneous displacement apparatus, nothing substantial has been found to obviate the discomforting postinjection headache. The displacement of the cerebrospinal fluid by gases other than air holds a little promise for less severe reactions, but headaches of moderate severity are still present in almost every case.

Summary. 1. The use of the simultaneous displacement apparatus has permitted the encephalography of 210 cases without fatality or serious accident.

2. Filtration of the gases through water before injection reduces the postinjection reaction and obviates the pleocytosis that often occurs with unfiltered air.

3. The substitution of other inert gases for air in encephalography makes for less severe headaches. Helium appears more promising than nitrogen in this respect.

NOTE.—The author wishes to express his extreme indebtedness to Dr. C. H. Lavinder, Senior Surgeon, U. S. Public Health Service, without whose kind interest and invaluable suggestions throughout the past 11 years this work could not have been carried out, and to Dr. J. D. Reichard, Surgeon, U. S. Public Health Service, in charge of Neurological Service, Ellis Island and Staten Island hospitals, for his full coöperation clinically.

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NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.*

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SINCE the introduction of diphtheria antitoxin peculiar and sometimes fatal sequelæ to injections have been observed, the most common of which is serum sickness. At first reactions of this sort were attributed to antibodies in the serum. Within a year, however, Johannessen¹ had disposed of that assumption by demonstrating that reactions of similar character followed the injection of normal horse serum.

In 1911 Vincent and Richet² published an account of a man, aged

* Read before the Neuropsychiatry Section of the California Medical Association at the Sixty-first Annual Session, Pasadena, May 2-5, 1932.

30 years, who had received 10 cc. of tetanus antitoxin under the skin of the abdomen. Nine days later he suffered from repeated episodes of malaise, vomiting, urticaria, syncope, shock and anuria. Fifteen minutes after the second episode paresis of the right arm set in. Subsequently examination revealed atrophy of the right supraspinatus and paralysis of the serratus anterior with reaction of degeneration (R.D.). Since that time there have been many contributions of similar character, particularly in the French literature. My own interest in this subject was awakened by a case of this sort which I saw on April 17, 1930.

Case Reports. CASE 1.—The patient was a man, aged 37 years, who had received a prophylactic injection of scarlet fever antitoxin in the lateral portion of the right arm 2½ months previously. Seven days after the injection the patient suffered from malaise, urticaria, abdominal cramps, fever and syncope. On the eighth day he complained of severe pain in both shoulders and within a few hours he noted weakness of the right shoulder. On examination there was almost complete flaccid paralysis of the right deltoid muscle and moderate weakness of the right biceps, brachialis, pectoralis major and scapular muscles. The right deltoid was rather tender and markedly atrophic. The right biceps reflex was not obtained; the triceps and supinator reflexes were normal. Sensation was intact throughout. On faradic stimulation of the right deltoid there was only a slight response from isolated bundles of the muscle. Eight months later the patient wrote that moderate improvement had taken place.

Through the courtesy of Dr. M. Stark, of Los Angeles, I recently had the privilege of examining a second case.

CASE 2.—The patient was a man, aged 25 years, who had received 4½ months previously a prophylactic injection of tetanus antitoxin near the insertion of the right deltoid muscle immediately following a slight injury to the right thumb. On the third day the right arm was swollen, red and itchy. Six days later the swelling, erythema and pruritus, which had persisted, spread rather rapidly over the entire body. Coincidentally the patient complained of excruciating pains through the shoulders and the pelvis. Two days later (11 days after injection of the serum) the erythema, swelling and pruritus subsided and the patient noted weakness of the right upper limb. The arthralgia persisted with diminishing severity for 1 month.

Examination revealed almost complete flaccid paralysis of the right deltoid and infraspinatus and moderate weakness of the right triceps and serratus anterior muscles. A few fibers of the anterior one-third of the deltoid could be contracted on effort. There was marked atrophy of the right deltoid and infraspinati and moderate atrophy of the serratus anterior. Over the lower two-thirds of the deltoid region there was partial anesthesia for light touch, superficial pain and warm and cold. The right deltoid, infraspinatus and serratus anterior showed partial R.D.

Review of the Literature. From the literature it has been possible to select 47 apparently authentic examples of neurologic complications of serum sickness which are presented in tabular form. Many of the reported cases, such as those of Etienne,³ have been excluded because they did not belong to this category or because of inadequate

descriptions. Cases following the use of vaccines have been omitted. Engelmann's case,⁴ often cited as the first to be recorded in the literature, is not included since there is no demonstrable relationship between the very mild serum reaction and the clinical picture of a slowly developing multiple peripheral neuritis which began 36 days later. In addition, I have excluded from consideration certain cases showing anaphylactic phenomena without serum sickness, such as that of Sheppe.⁵ Because of the character of the clinical findings, the time relationships and the fact that mild cases of serum disease may be overlooked, 3 cases have been included in this series in which there are no definite data descriptive of serum sickness.

Analysis of the Cases. From a study of Table 1 it is apparent that males have been much more frequently involved than females. This may be attributed to the fact that men are more exposed to injuries necessitating prophylactic injections of tetanus antitoxin than are women. Of the 7 patients who developed neurologic complications following injections of diphtheria antitoxin, 4 were males and 3 were females. All of the patients in this series, however, who received scarlet fever antitoxin were males. That the disease occurs chiefly among adults is shown by the average age (26.9 years) of the group. To be precise, 33 of the 47 patients whose ages are recorded were 21 or more years of age.

TABLE 1.—NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.

Number of cases reviewed	49
Sex distribution:	
Males	44
Females	5
Average age in years (46 patients)	26.9
Average interval in days between first injection and onset of serum sickness (39 cases)	6.8
Average interval in days between onset of serum sickness and the neurologic complication (35 cases)	2.1

TABLE 2.—NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS.

Serum injected	No. of cases.
Tetanus antitoxin	34
Diphtheria antitoxin	7
Scarlet fever antitoxin	5
Antipneumococcic serum, Type I	2
Antimeningococcic serum	1
Total	49

The average interval between the onset of serum sickness and the appearance of neurologic complications is difficult to determine accurately. In many instances arthralgia has been so severe as to be almost incompatible with physical effort. In the 35 cases, concerning which data of this sort are recorded, the interval was

approximately 2 days. In 13 instances the serum sickness seems to have been relatively mild, in 23 moderately severe and in 10 very intense. The average length of the serum disease in the 12 cases in which the duration was recorded, was approximately 3 days. From Table 2 it will be seen that 34 of the 49 cases developed evidence of neurologic complications following the injection of tetanus antitoxin. This is probably to be attributed to the fact that serum of this sort is most often given to adults who in turn are more likely to develop neurologic complications.

Apparently the brain, the spinal cord, the meninges, the nerve roots, the cords of the brachial plexus or the peripheral nerves may be involved directly by urticarial edema analogous to that in the skin. It has frequently been assumed that the urticarial lesion was located in one or more of the spinal foramina. Sicard and Cantaloub⁶ suggested that certain cases of mononeuritis might be due to compression of a nerve as a result of an urticarial process within an aponeurotic sheath (neurodocitique).

In the majority of instances nervous structures associated with the brachial plexus have been involved (Table 3). In all of these cases there was disturbance of motor function; in about one-fourth of the cases there were sensory changes. The plurality of these cases showed involvement of the fibers derived from the fifth and sixth cervical nerves. To explain the unusually frequent involvement of the upper two nerve roots of the brachial plexus, Bourguignon⁷ advanced the hypothesis that tetanus antitoxin selects nerves with low chronaxie while diphtheria antitoxin selects those with medium chronaxie. A casual analysis of the cases shows that this suggestion is untenable.

TABLE 3.—DISTRIBUTION OF THE NEUROLOGIC COMPLICATIONS OF 49 CASES OF SERUM SICKNESS.

Superior brachial plexus—unilateral motor	13
Mononeuritis (radial, 7; long thoracic, 1)	8
Optic neuritis	6
Brachial plexus—bilateral motor	4
Brachial plexus—bilateral sensorimotor	4
Superior brachial plexus—unilateral sensorimotor	4
Superior brachial plexus—bilateral motor	3
Superior brachial plexus—bilateral sensorimotor	3
Brachial plexus—unilateral motor	1
Brachial plexus—unilateral sensorimotor	1
C.N.S., meninges, brachial plexus—bilateral motor	1
Urticarial edema of the brain and meninges	1

Sainton⁸ has pointed out that the process may not involve equally all fibers of a given muscle but may spare bundles of varying size. This was true in both of my cases. Profound changes in the electrical reactions, particularly in the distribution of the fifth and sixth cervical nerves are not uncommon.

TABLE 4.—ABSTRACTS OF 47 CASES OF NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS FROM THE LITERATURE.

Author.	Sex. Age.	Serum used.	Dosage.	Site of injection.	Serum reaction.		Evolution of neurologic complications.
					Days after injec- tion.	Manifestations.	
Vincent and Richet, <i>filis</i> ² Thacon: <i>Rev. de méd.</i> , 1912, 32, 749 Cauchois: <i>Bull. et mém.</i> <i>Soc. de chir.</i> , 1912, 38, 826 Dyke: <i>Lancet</i> , 1918, 1, 570	M 30	Tetanus, inject. 4 yrs. prev.	10 cc.	Under skin, belly	9	Mal., vom., u., syne., shock; repeated episodes with an. E., u., tachycardia, oliguria; dur. 3 days	15 min. after 2d episode, par., rt. arm; p., ser. ant. with R.D.; atr. of S.S. P. of ser. ant. with R.D., amy. beginning on 3d day.
	M 30	Tetanus	10 cc.	9		
	M 45	Tetanus	20 cc.	Right thigh	1	F., pr., arth., rt. shoulder	Par. and anes., dorsum rt. index finger and thumb; par. rt. upper limb; atr., triceps and I.S.; 18 mos. later residuals.
	M	Tetanus	750 U. 750 U. 500 U. 16,000 U. 16,000 U. 10 cc.	Right breast	13	2 days before last inj., pain, stiffness, rt. shoulder; dur. 4 days	Jan. 3: inability to abduct rt. arm. on 5th day; Mar. 9: atr. with R.D. rt. del., S.S. and I.S.
Halipré, Goujard: <i>Nor- mandie méd.</i> , 1920, 31, 293 Marchal: <i>Arch. méd. de belges</i> , 1921, 5, 406	M 50	Tetanus	10 cc.	Left thigh	5	U.; gen'l'd pain; dur. 4 days	Same date: arth. rt. shoulder with droop- ing; winging, rt. scapula; atr., I.S. and S.S.
	M 22	Tetanus	10 cc.	On 8th day w., left shoulder and rt. arm; 2 days later drooping shoulders with p. of abductors of arm; later p. rt. serratus ant. and I.S. and S.S. bilat.
	M 23	Tetanus; prev. inj. at 8 yrs.	10 cc.	7	F., u., pr.; dur. 4 days	On the 4th day pain, both shoulders; ina- bility to abduct arms; winged scapula, bilat. foll. by atr., trapezius and I.S. and S.S.; weakness, ericthyroid mus- cles; sensory loss over arms and scapulae.
	M 25	Antipneumo- cocci Type I	200 cc. 100 cc. 100 cc. 100 cc.	Intraven- ously	8	F., 101° F.; gen'l'd rash	Hyperemia and swelling of optic disks 1 D.; c. of retina; veins engorged, arter- ies normal; restoration to normal in 3 mos.
Mason: <i>J. Am. Med. Assn.</i> , 1922, 78, 88	M	Antimeningo- cocci	...	Intraspin- ally	..	Gen'l'd serum sickness	Optic neuritis without visual disturb- ance; dur. 15 days; C.S.F., 15 cells.
	F 38	Antipneumo- cocci Type I	300 cc.	Intraven- ously	..	Gen'l'd serum sickness	Mild optic neuritis; C.S.F., 12 cells.

Mouriquand, Dechaume, 1923, 123, 751.	F 34	Diphtheria anti- toxin	20 cc.	Abdomin- al and gluteal muscles	4	F.; arth.; eruption with e.; dur. 4 days	On 3d day w. rt. area and shoulder, flex- ors, extensors, forearm; atr. del., I.S.
Morichau-Beauchant: Arch. méd. chir. prov., 1923, 13, 395	M 43	Tetanus	10 cc.	Inner as- pect, left thigh	8	F.; marked u.: arth.	2 days later pain, upper limbs; next a.m., p., muscles both upper limbs with R.D. over r. distributions; dur. rt. 1 wk.; rm. 1 yr. later.
Sieard, Cantaloube	M 55	Tetanus	20 cc.	Right thigh	9	Erythema, local e, pr arth.	2 days after onset, pain along r. n. foll. by comp. wrist drop, left.
Lafourcade, Terris, Sou- ques; Bull. et mém. Soc. méd. d. hôp., 1924, 48, 757	M 24	Diphtheria	20 cc.	Left flank	8	Erythema, u. and e., eyelids, face and limbs	On 3d day pain along left r. n. with comp. r. n. p.; biceps sl. involved; dur. 18 mos.
Sainton, Descouts, Le- Clerc	M 33	Tetanus	20 cc.	Left flank	8	Arth., erythema u. and e., face and glottis	On 3d day intense pain left arm foll. by typical r. palsy.
	M 29	Tetanus	10 cc.	Right thigh	6	U., beginning at site of inj., becoming gen'l'd; dur. 5 to 6 days	Toward end of serum reaction, w. upper limbs bilat. with atr. of shoulders, arms, forearm and hands; improve- ment.
Lhermitte: La Pratique méd. français, 1924, 1 300	M 48	Tetanus; previ- ous inj. 6 mos.	4	4 days after last inj. pain, shoulders; malaise, f. and e. of belly	Simultaneously w. upper limbs: fibrillary twitchings, triceps; partial R.D. rt. tri- ceps; hypocoaxitability, delt. and girdle muscles.
	M 22	Tetanus	10 cc.	Under skin, ab- domen	4	Arth., rt. shoulder	Winged scapula; later atr. musculature of shoulder girdle; improvement.
	M 23	Tetanus	10 cc.	9	Urticarial eruption with dyspnea	1 day later arth. rt. shoulder with p. abduction, arm and supination, fore- arm; atr. I.S. and S.S.
André-Thoumns: Presse méd., 1925, 33, 217	F 26	Diphtheria	40 cc. 20 cc.	Buttocks	8	F.; u.; arth., esp. upper limbs; dur. 3 days	W., del., I.S. and S.S. scapula R.D.
Binet, Hoche: Rev. méd. de l'est, Nancy, 1925, 53, 741	M 35	Tetanus	10 cc. 10 cc.	Arthralgia	On 4th day inability to raise or rotate rt. arm; atr. rt. del., esp. post. 3d; dimin- ished sensibility rt. 5th cerv. root area; loss, pilomotor reflex over anes. area.
Brown: Am. J. Ophth., 1925, 8, 614	M 12	Diphtheria	10,000 U.	Intraven- ously	Shortly, pain rt. scapular and biceps regions, left shoulder and arm; by 15th day unable to abduct arms; 6 wks. later Pinkish optic disks; hazy margin; hyper- emia of retina with exud.; dur. 28 hrs.
	M 21	Diphtheria	10,000 U.	Intraven- ously	8	Fever, urticaria, pruritus	Optic neuritis; violent conjunctival reac- tion; dur. 28 hrs.

F. fever; w., weakness; p., paralysis; atr., atrophy; u., urticaria; arth., arthralgia; pr., pruritus; n., nerve; del., deltoid; S.S., supraspinatus; I.S., infraspinatus; r., radial; dur., duration; e., edema; bilat., bilaterally; par., paresis; inj., injection.

TABLE 4.—ABSTRACTS OF 47 CASES OF NEUROLOGIC COMPLICATIONS OF SERUM SICKNESS FROM THE LITERATURE—Continued.

Author.	Sex. Age.	Serum used.	Dosage.	Site of injection.	Serum reaction.		Evolution of neurologic complications.
					Days after injec- tion.	Manifestations.	
Leri, Escalier. Bull. et mém. Soc. d. hôp., 1926, 42, 1408	M 38	Tetanus	10 cc.	Right buttock	5	F., arth., swelling at site of inj.	2 mos. later wife observed winged scap- ulae; also had atr. rt. del. and lt. I.S. and S.S.
Enguet: Gaz. heb. d. Soc. méd., 1926, 46, 404	M 25	Tetanus	10 cc.	Int. sur- face, left thigh	9	Arth., lt. shoulder, neck and rt. upper limb	Next day flaccid p. upper limbs, lt. more than rt.; hypesthesia to touch, lt. upper R.D. extensors, hands, fingers; improv.
Verger, Autherlin, Del- mas, Marsalot: Rev. de méd., 1927, 44, 451	M 20	Tetanus	10 cc.	Subcutan- eous	8	Pr. and e. at site of inj.; dur. 1 day; C.S.F. 30 lymph.	Following day pain, both shoulders, with p. both upper limbs, esp. rt., and aboli- tion, tendon reflexes; winged scapulae; atr., lt. biceps and I.S. and S.S.; hyp- esthesia both limbs R.D.; improv.
Faure-Benulieu: Presse méd., 1927, 35, 1419	M 25	Tetanus	20 cc.	6	E. of face; gen'l'd u.; dur. 2 days	Simult. gen. w.; impr. in 10 days but ser- atus magnus p. and I.S. and S.S. atr.
	M 52	Tetanus	...	Left thigh	12	U. at site of inj.	2 days later pain in all extrem., subseq. p. rt. arm foll. by atr. and R.D. of del., S.S. and I.S.; zone of anes. dorsal aspect entire rt. upper limb.
Gordon: Med. J. and Rec., 1928, 127, 330	M 9	Scarlet fever	250 U.	Left deltoid	2	F., u. at site of inj.; pr.	1 day later flaccid p., dist. r. n., reflexes dim.; sta. 3 wks.; later comp. recov.
	M 11	Scarlet fever	250 U.	Right deltoid	10 hrs.	Violent pr., entire rt. upper limb; burn. and ting. for m.	Flaccid p., muscles innervated by r. 24 hrs. later; sta. 3 wks.; later com. recov.
Bourrat: Lyon méd., 1929, 143, 787	F 22	Tetanus	E. and rubor pr.; headache	Orbital pain; amblyopia; central scotoma rt. eye; hyperemia of disk with venous engorgement; dur. 12 days.
Kennedy ¹⁰	M 36	Tetanus	10 cc.	10	Pain, both upper limbs	W. extensors, wrists and fingers; 1 mo. later p. extensors of wrist and supina- tors; more marked, rt.
	M 15	Tetanus	...	Left arm	..	U., arth., swelling rt. arm	Par. of abduction, rt. arm; p., rt. serra- tus magnus on 9th day after inj.
	M 21	Tetanus	...	Left arm	7	Eryth. rash about site of inj.; arth., rt. shoulder	3 days later w., rt. shoulder and winged scapula.

M 11	Scarlet fever	4	Fever, 104° F.; urticaria	Almost at once headache, meningitis, cry and retrac. of head; Kernig's sign; rt. homonymous hemianopsia, total alex. and ar. aphasia; partial rt. hemiplegia and aphasia; swelling, both optic disks; C. S. F. press. incr.; 14 lymph.; dur. 4½ wks. Coincidentally numbness with total anesthesia rt. circum. area; p. abduc. of arms with wasting, both del. and I.S. and S.S. bilat.; comp. R.D., del.; partial, scapular muscles; hypesthesia lt. circumflex area; improvement in 1 yr. Inability to abduct arms; atr., both del.; decreased sensibility, both circumflex areas; incomp. R.D.; improv. in 6 mos. 2 days later p. rt. serratus ant. and par. rt. trap.; partial R.D., affected muscles. Next day p. rt. arm; foll. day p. lt. arm and par. both lower limbs; 2 mos. later atr. p. rt. upper limb; par., lt. upper limb; bilat. Babinski; p. lt. abductors. Gen'l w., r. arm; mod. atr., rt. S.S. and I.S. muscles.
M 18	Scarlet fever	Fever, urticaria, arthralgia	
M 12	Tetanus	Fever, urticaria, arthralgia	
M 10	Tetanus	10 cc.	...	8	U., next day transient trismus, pain in rt. shoulder	
M 8	Tetanus	11	U., cervical rigidity, Kernig's sign, pain in neck and arms	
F 77	Diphtheria	...	Right buttock	3	Arth. followed by swelling of hands	
M 40	Tetanus	1500 U.	Anterior abdominal wall	6	Gen'l'd u.; 3 days later arth. and tingling and swelling feeling, fingers and wrist	
M 7	Tetanus	1500 U.	Left deltoid	7	Arthus' phenomenon; arth.	
M 17	Tetanus	...	Intramuscular, lt. thigh	6	Swelling, rt. knee and thigh with severe local reaction; arth.; upper limbs for a fortnight	
M 31	Diphtheria	10	Pain, neck to elbows, more severe, rt.	
M 40	Tetanus	1500 U.	Left infra-scapular	4	Hives for 2 or 3 days foll. by arth.	
M 40	Tetanus	1500 U.	Left deltoid	4	Erythema, vesicles, pr., e. and arth.; dur. 3 days	
F., fever; w., weakness; p., paralysis; atr., atrophy; u., urticaria; arth., arthralgia; pr., pruritus; n., nerve; del., deltoid; S.S., supraspinatus; I.S., infraspinatus; r., radial; dur., duration; e., edema; bilat., bilaterally; par., paresis; inj., injection.						3 days later arth. and tingling and swollen feeling, fingers and wrist; lt. impr. quickly; l., rt. grip; dimin. reflexes, lt. and absent reflexes, rt. upper limb. Lt. r. palsy, 1 day later; reflexes and sensation norm.; comp. recov. in 6 wks. W.; both arms, became apparent as pain disappeared; R.D. rt. del. I.S. and S.S. and lt. del.; analgesia and thermesthesia rt. axillary n. area. 3 wks. later marked atr. rt. and sl. lt. del. with corresp. degrees of sensory loss over axillary n. areas. P. lt. del. I.S. and S.S. with R.D.; impr. 4 mos. later; comp. recov. 1 yr. later. On 7th day w. of rt. arm; atr. and R.D. rt. del. muscle; dimin. sensory distribution over rt. axillary n.

Baudouin, Hervy: Rev. neurol., 1931, 1, 306
Bourignon: Rev. neurol., 1931, 1, 334

Wilson, I. J. Am. Med. Assn., 1932, 98, 123

Young: J. Am. Med. Assn., 1932, 98, 1139

Fibrillary twitchings of the triceps were observed in the case reported by Sainton, Descouts and LeClerc.⁹ There is matter for argument here as to whether the fibrillations were indicative of direct involvement of the cells of the anterior horn of the spinal cord or whether they were due to retrograde changes dependent upon damage to the anterior roots. Kennedy's case¹⁰ showed evidence strongly suggestive of edema of the brain and meninges. Despite the severity of the symptoms and signs, most of the cases recover completely.

Comment. It is common knowledge that the incidence of serum sickness is intimately related to the amount of serum injected. In Weaver's series¹¹ 10 per cent of the patients receiving less than 10 cc. of serum developed serum sickness while 75 to 100 per cent of those receiving 90 cc. or more showed evidence of serum disease. Serum derived from certain horses is more likely to be followed by serum sickness than that obtained from others. Following the use of sera that have not been heated or that are less than 2 months old¹² serum sickness occurs with unusual frequency and severity. There is also a personal equation: individuals react differently following injections of serum obtained from the same source.

No data as to the relative frequency of the neurologic complications are available. It should be emphasized that while cases of this sort are of clinical and medicolegal importance, the occurrence of complications of such rarity should not be construed as a contra-indication to the judicious prophylactic or therapeutic use of sera.

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CONGENITAL HEMIHYPERTROPHY: A REPORT OF EIGHT CASES.

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IN 1926 one of us (E. W.) reported a case of congenital hypertrophy which involved the left part of the shoulder girdle, left arm and left hand. At that time, in the literature of the Surgeon-General's Library there was a total of 195 cases of congenital hemihypertrophy, 44 of which involved a whole side of the body. Since 1926 about 28 cases of the latter group have been reported.

An analysis of these cases from the literature gives the impression that the term congenital hypertrophy is used to denote a chaotic, bizarre syndrome, with but one constant feature; namely, increase in size of the involved parts. There is no reason to believe that this increase is compensatory hypertrophy. Usually there is no evidence that the enlarged part possesses greater strength or power, although the patient whose case was reported in 1926 felt that the involved part was the stronger.

The 8 patients whose cases form the basis of this report ranged in age from 3 to 32 years (Table 1). There were 5 males and 3 females. The right side was hypertrophied in 4, the left in 3, and in 1 the hypertrophy was crossed. The difference in the size of the extremities, as revealed by measurements, is often small, in fact it is usually less than it appears to be from general inspection of the patient. The most interesting case in this group, on account of its rarity, was that in which the hypertrophy was crossed (Case 8). There was no difference in the length of the arms and legs. The hypertrophy seemed to be mainly of the muscles. Consequently the disproportion in size was most conspicuous. The mental status was normal in 6 cases, 1 patient was mentally deficient, and the mentality of 1, who was mute, remained unknown. No history of congenital familial anomalies was obtained. Widespread congenital nevi were present in Cases 6 and 7. Case 1 presented 2 other congenital anomalies besides hypertrophy, namely, hypospadias and cryptorchidism. This child had also been suspected of having a congenital heart lesion at the time of his first visit to the clinic. This, however, had given no symptoms. A definite diagnosis of congenital heart lesion was made in Case 4. Cryptorchidism was also present in Case 7 and polydactylism in Case 4.

TABLE 1.—SUMMARY OF 8 CASES.

Case.	Age, yrs.	Sex.	Height, cm.	Weight, kg.	Hypertrophied side.	Difference in circumference of extremities, cm.				Difference in length of legs, cm.	Mental status.	Comment.
						Upper part of arm.	Lower part of arm.	Thigh.	Calf.			
1	3 7	M ..	87 125	14.0 25.0	Left 0.5	1... 1.5	2.0 3.0	1.5 1.5	1.0 1.0	Normal	Hypospadias, cryptorchidism; questionable congenital heart disease; good general health.
2	4 9	F ..	130	15.0	Right	2.0	2.5	1.0 2.5	0.5 3.2	2.5	Normal	Good general health.
3	9	M	115	20.0	Right	1.0	1.0	2.0	2.0	..	Unknown (mute)	Good general health.
4	14	M	147	41.7	Left	2.0	Normal	Congenital heart disease; polydactylism; orthopedic shoes fitted.
5	18	M	170	72.7	Right	2.5	3.7	7.5	1.3	..	Normal	Good general health.
6	23	F	165	58.0	Right	2.0	1.5	7.0	5.0	..	Deficient	Extensive nevus over body; good general health.
7	23	M	172	69.9	Left	2.0	2.0	10.0	6.0	..	Normal	Extensive nevus over body; hypertension, cryptorchidism.
8	32	F	153	60.0	Crossed	2.0	1.0	4.0	6.0	..	Normal	Left arm and right leg hypertrophied.

In Fig. 1 are given comparative measurements of size of corresponding parts on the two sides of the body. The differences in the ears, palpebral slits, nares, third fingers, and feet may be noted in the chart of Case 6. The photographs of patients (Cases 1 and 6) show the range of the hypertrophy. In Case 1 it would not be noticeable if it were not for the tilting of the pelvis, whereas in Case 6 it is obvious.

As a rule, obvious unilateral enlargement of a part or parts is of casual significance to a patient until something goes wrong. Difficulty in obtaining shoes and gloves to fit has caused little or no concern. With the patient who has become invalided on account of monstrous unilateral development, unequal growth has caused concern from birth; these are the unusual cases, which are similar to those first reported.

In a well-developed case of congenital hypertrophy, the resulting disproportion in development is grotesque. The hypertrophied parts often appear to "sag," are coarse, and lack symmetrical proportions in themselves. On the hypertrophied side there may be normal fingers and toes besides those that are hypertrophied. Crumpled toes, deformed from ill-fitting shoes, are mute evidence of the complaint that "the shoe on that foot has always been a little tight." The skin over the hypertrophied parts is normal in texture. There may be increased dimpling at the elbows, the distribution of the hair and other appendages of the skin is usually within normal

limits, occasional nevi may be present, and dentition on the involved side is precocious. Compensatory scoliosis and tilting of the pelvis in an attempt to compensate for the longer leg are common. If the compensation is not sufficient, limping and sciatica result.

The etiology is not known. The asymmetry begins in early embryonic growth and development. Phisalix obtained a 10 mm. human embryo which was asymmetric. Gessell has carefully reviewed the evidence which is in favor of the anomaly being a process of twinning. Many other hypotheses and suggestions have

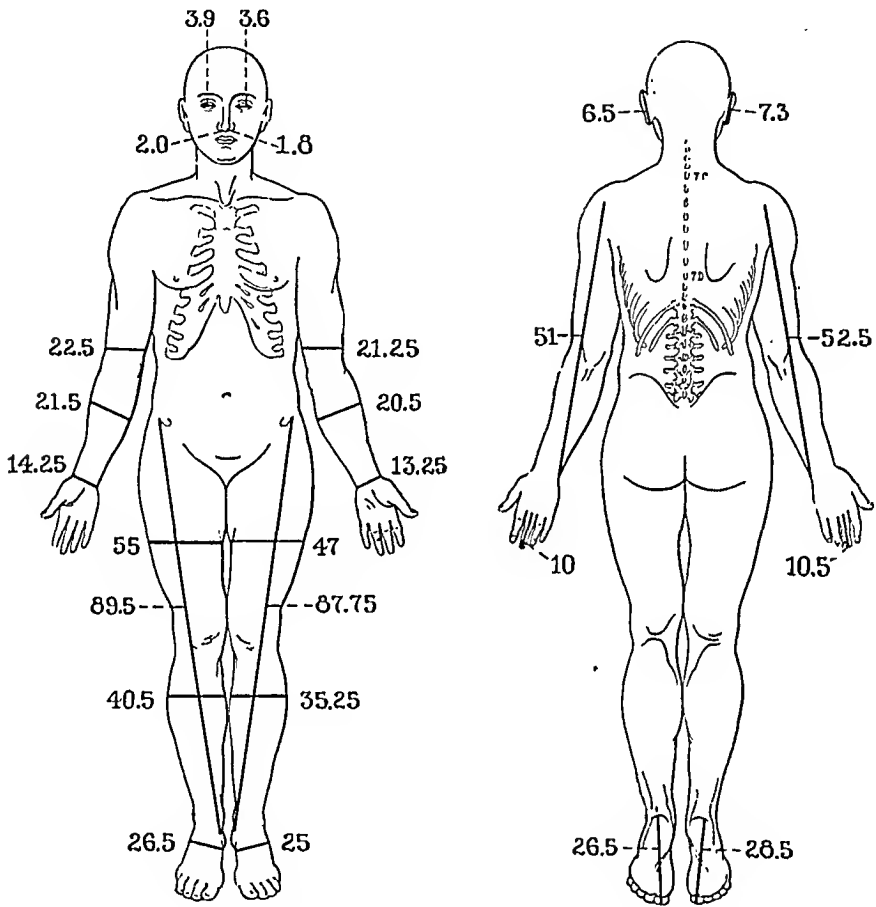


FIG. 1.—Diagrammatic drawing of patient in Case 6.

been offered, but none is more than a conjecture. Apropos of this, Jenkins once remarked, "The wonder is not that the two sides of the body are dissimilar, but rather, that they are ever alike."

A general description has been given. As to diagnosis, certainly if the hypertrophy occurs in the arm or leg, one must rule out congenital arteriovenous communication which is associated with enlargement of the part involved. Lymphedema is likewise eliminated without difficulty, since there is no edema, and if any doubt exists, a period of rest in bed, with elevation of the involved part,

should settle the question. The diagnosis should offer little difficulty if the possibility of hemihypertrophy is kept in mind, after careful neurologic examination to rule out hemiatrophy.

If the hypertrophied parts reach incompatible proportions in early life, the outlook for orthopedic correction is bad. Since the growth of the enlarged side continues throughout the period of normal development it may require correction in the second decade. Usually the anomaly does not cause discomfort.

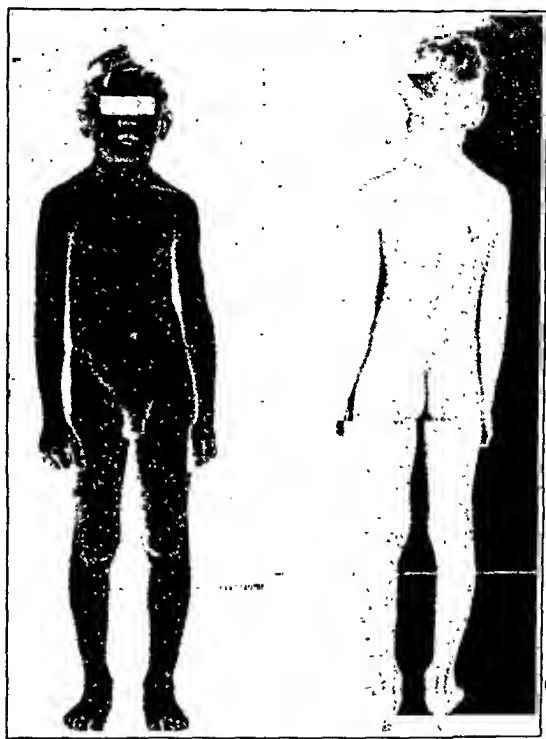


FIG. 2.—Photograph of patient in Case 1.

Case Reports. CASE 1.—This boy (Fig. 2), aged 3 years, was brought to the Mayo Clinic with the complaint that one leg was larger than the other. He also had pain in the knees. Birth had been normal, with a vertex presentation; labor, easy, and the birth weight, $7\frac{3}{4}$ pounds. The boy was breast fed for 1 year. He sat alone at 6 months, and walked and talked at 18 months. He was a "big, strong baby," and for the first year and a half he was perfectly well in every respect. Disproportion in the two sides of his body had been noticed some time before the age of 18 months; the left side was the larger. He had always been susceptible to colds. At 18 months he had an infection in the throat and a cutaneous eruption which was thought to be measles. At 2 years and 9 months he had a similar attack. At the age of 2 years the enlargement of the left side of the body was definite, and 10 months later he began to have pains in his knees, without swelling or stiffness. There was some restlessness and occasional crying at night.

The boy was well developed and nourished, alert, active and coöperative. The left side of the head and face was definitely larger than the right. The heart was not enlarged, and there were no thrills, but there was a loud systolic murmur well transmitted to the axilla. Hypospadias was present and the testes were not well descended; the right one was felt with difficulty. The left leg was definitely longer and larger than the right, and there was no edema. Reflexes were equal. Urinalysis, von Pirquet test, and roentgenograms of the chest gave negative results. The value for hemoglobin was 60 per cent, erythrocytes numbered 3,350,000, and leukocytes 4600 per c.mm. of blood. Examination of the nose and throat revealed fibrous tonsils of medium size.

CASE 2.—This girl, aged 4 years, had been born at term, weighing 10 pounds. Labor had been moderately long but delivery normal. The child had been breast fed for the first 12 months, had her first teeth at 1 year, began to walk at about 10 months, and talked at 18 months. The mother noticed that when the child was 2 years old she limped. The left leg and left arm were smaller and shorter than the right. The limp gave no discomfort and did not interfere with motion. She ran and played without difficulty, having equal use of the two sides of the body. She never had paralysis, convulsions, or unconsciousness of any kind. Her general health was excellent.

The child was well nourished and well developed except that the right side of the body, and face, right leg and right arm were larger than the left. The pupils reacted normally, the tonsils were small, and the heart, lungs and abdomen were normal. Urinalysis, blood counts, estimation of hemoglobin, von Pirquet tests, and roentgenograms of the bones did not give evidence of anything unusual.

At the age of 9 years this girl was in good general health. Her right leg had continued to increase in length until she had difficulty in walking. There was marked scoliosis.

CASE 3.—A boy, aged 9 years, had a family history which was entirely unimportant except for the fact that his mother had had two prematurely born babies. The patient had been born at 7 months, a twin, and had weighed 2½ pounds. He was bottle fed at first, then breast fed. He was weaned at 2 years, at which time he had had a severe illness with "spasms" and could not keep anything on his stomach. His condition gradually improved, and he had had no convulsions for 4 years before we saw him. From birth the patient's left side had seemed larger than the right.

The child was small for his age. His head was narrow in the bitemporal diameter and long in the fronto-occipital. The pupils reacted, and the thyroid gland was negative to examination. The first heart sound was indistinct, but the sounds were regular. The left foot was smaller than the right, and the left leg shorter than the right. Urinalysis, blood counts, estimation of hemoglobin, Wassermann test, von Pirquet test and roentgenograms of the chest were negative. Ophthalmoscopic examination disclosed normal fundi. Examination of the ears, nose, and throat disclosed complete deafness in both ears. Roentgenograms of the head revealed a normal sella turcica.

CASE 4.—A boy, aged 14 years, was brought to the clinic complaining of lack of "pep," and of rheumatism. Birth and development had been normal except for polydactylism. He walked and talked at the age of 1 year and had his first teeth before he was a year old. He was in the eighth grade in school when we saw him. Aside from the enlargement of the left side of his body his general health had been considered good previous to the onset of the illness for which he was brought to the clinic. He was said to have had an attack of rheumatic fever of 6 weeks' duration 4 years before, and about 6 months after that his tonsils and adenoids had been

removed. Since that time he had limited his activities and had been very comfortable. In the 18 months before we were consulted he had had no "pep," his knees and feet had been sore, and there had been swelling of the ankles. The disproportion in the length of his legs had been corrected by special shoes.

The patient was well developed and well nourished. There was the appearance of slight fullness in the left side of the face and chest, and generally in the left arm and leg. The eyes were rather wide apart, which seemed to exaggerate the asymmetry of his face. The heart was not enlarged and its sounds were regular and clear. There were definite sinus arrhythmia and forced respirations. A loud systolic murmur was well transmitted to the axilla. Blood pressure was systolic 120 and diastolic 80. Urinalysis, blood counts, Wassermann test of the blood, von Pirquet test, Widal reaction, examination of ocular fundi, and roentgenograms of the teeth and sinuses gave essentially negative results. Roentgenograms of the cervical region gave evidence of a cervical rib on the right, and roentgenograms of the hands disclosed apparent developmental anomalies of both thumbs, marked dislocation of the phalangeal joint on the left, and anomalies of the metatarsal bone.

CASE 5.—A youth, aged 18 years, gave a family and past history not relevant to his complaint. His chief trouble was that his "left leg was too long" and ached when he walked; he had to lean to the right side in order to walk with comfort. There had been no other difficulty with the right leg, such as weakness, or pain in the hip or knee, and there was no swelling.

On general examination the patient appeared healthy. The left side of his face, and his left arm and left leg were developed out of proportion to the right. Strength on the two sides of the body was practically equal, and all motions of the joints were good. The pupils reacted normally. He had had much dental work, and the tonsils were small. The heart was not large, and there was a systolic murmur to the right of the sternum which was poorly transmitted. Blood pressures were systolic 155 and diastolic 88. The bones of the pelvis, and the femur, were reported normal. Urinalysis and Wassermann test of the blood gave negative results. The orthopedist gave him a pair of shoes which raised the heel of his right foot about $1\frac{1}{2}$ inches. About 3 months later the patient returned and reported that he had received considerable relief.

CASE 6.—A woman (Fig. 3), aged 23 years, came to the clinic complaining of intermittent fronto-occipital headache and of difference in the size of the two sides of the body. From birth, the right side, including the face, right arm, and right leg had been larger than the left. This had not given her much concern and had caused no disability. She had been unable to finish the grade school. She had had pain in the right lower part of the abdomen and right thigh all of her life. For 6 years she had had headaches, which had been worse in the previous 2 years. There had been some blurring of vision associated with the headache. The family and past histories were negative. The patient had been married for 2 years without becoming pregnant.

The patient was well nourished; the right side of the face, the right arm, the right mammary gland, the right labia and the right leg were distinctly larger than the left. There was a large, flat, soft elevation on the right lumbar region 10 by 12 cm. A large superficial nevus was present over the chest and upper lumbar region. Neurologic examination revealed a mental age of 9 years according to Terman's revision of the Binet-Simon test. Mild secondary anemia was present. Urinalysis and the Wassermann test of the blood gave negative results. The basal metabolic rate was normal. Roentgenograms of the bones disclosed no differences in the two sides except in the pelvis, where there was lack of development of the left side.

CASE 7.—A man, aged 23 years, came to the clinic complaining of high blood pressure. Other members of the family were free of congenital defects or malformations. About a year previous to the patient's coming to the clinic, in his last year in college, he began to have pain across the front of his head. These attacks came every week or two and were accompanied by nausea and vomiting. The blood pressure was found to be elevated, and it was for a general survey of his condition that he came to the clinic.

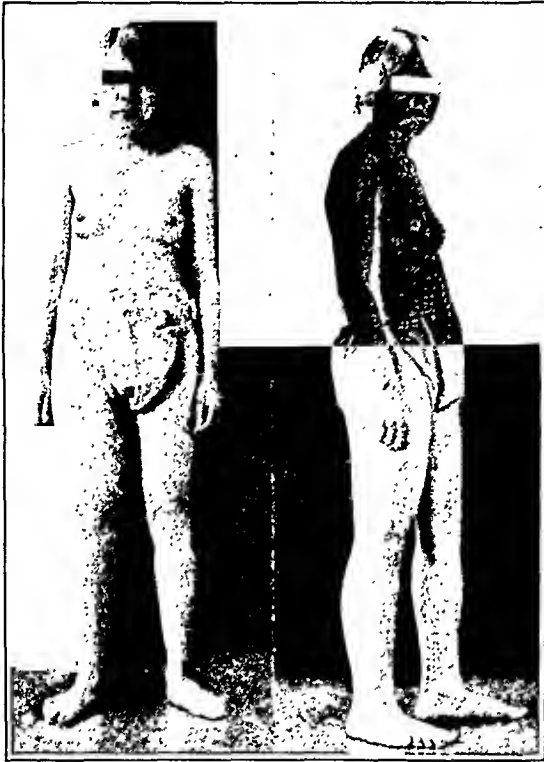


FIG. 3.—Photograph of patient in Case 6.

The patient's left leg and the left side of his body were larger than the right. There were extensive congenital nevi over the thorax. The pupils reacted normally, the heart measured 3 by 11 cm., and the blood pressure was systolic, 185; diastolic, 100. The lungs were clear. The right testis was undescended. General neurologic examination gave negative results, and results of laboratory tests were unimportant.

CASE 8.—A woman, aged 32 years, came to the clinic giving a family and a past history which were entirely without significance. She was married and had 2 normal children. Since the age of 5 years the *right* leg had been the larger, and for an indefinite period this also had been true of the *left* arm.

The patient was well developed and well nourished. The *left* arm and the *right* leg were decidedly the larger, but the face and the head were symmetrical. Blood pressure was normal, reflexes equal and active, and there was no edema. General neurologic examination, urinalysis, blood counts, and Wassermann tests, all gave negative results.

Summary. The 8 cases of congenital hemihypertrophy reported in this paper added to those that have been reported before make

80 cases recorded in the literature. Included in the 8 cases is 1 case of congenital crossed hypertrophy. Diagnosis is not difficult if the possibility of congenital hypertrophy is considered when there is unilateral enlargement of a part. The anomaly is often accompanied by other congenital or developmental features of note. The prognosis depends on the degree of hypertrophy and the age of the patient. After normal growth is finished, if there is no disability, there is no reason to expect any disability to occur.

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HYPOGLYCEMIC CONVULSIONS WITH HYPOPLASIA OF THE PANCREAS.

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THE syndrome of hypoglycemia, not due to administration of insulin, was described by Harris,¹ in 1924. Since the appearance of his paper there have been many reports of cases in which the blood sugar has been found at low levels. According to the apparent etiology these fall into three groups: (1) Those cases in which there is a tumor of the pancreas involving the islets. Wilder, Allen, Power and Robertson² reported the first case of this kind. Carcinoma of the tail of the pancreas was found at autopsy. It was possible to prove the presence of insulin in the metastases from this growth. (2) Hypoglycemia in which exploration has shown an apparently normal pancreas. Finney and Finney³ reported a case in which the removal of a portion of the pancreas was followed by clinical improvement. (3) Hypoglycemia attributed to other factors such as menstruation, functional or nervous disturbances and excessive carbohydrate intake. Anderson⁴ reported a case in which there was an adenoma of the suprarenal gland. Harris⁵ has recently given an excellent review of the American cases to date.

The patient with whom this report is concerned had prolonged hypoglycemia with the blood sugar rarely rising above subnormal levels. She had repeated convulsions and the operative findings

in regard to the pancreas apparently establish an additional possibility for hypoglycemic states.

Case Report. The patient, Mrs. R., aged 30 years, was referred by Dr. W. H. Bennett of Lamesa, Texas. She complained of attacks of weakness and her husband stated that practically every night she had a convulsion lasting from 10 to 30 minutes. She was well until the age of 13. At that time she became overheated and was sick for several weeks. At 15 her appendix and right ovary were removed. Following this, at her menstrual periods she had "nervous spells" with uncontrollable jerking of the arms and legs. Her periods were regular, of the 28-day type, but scanty, lasting not more than 2 days. After marriage and the birth of her first child, she was well until the birth of her second child, at which time she had mastitis. Shortly thereafter, she began to have attacks of "blank spells." These lasted only a few minutes but were frequent. She then developed periods of weakness occurring late in the day or at night and 3 years ago lapsed into a stuporous condition which was more or less complete for 52 hours. Her physician correctly diagnosed this as hypoglycemia. The administration of glucose intravenously produced prompt recovery. He advised frequent feeding of sugar. This improved her condition somewhat.

She now does well during the daytime, but at night, most frequently at 1 or 2 A.M., she becomes restless, develops a cough, makes purposeless movements, and cannot be aroused. Salivation is marked at this time. If orange juice can be given, the attack is short, but at times it is impossible to induce her to swallow and in that case the attack may be prolonged and severe. Several times there have been severe convulsions with definite clonic spasms. At intervals, even when there are no convulsions, she complains of headache, drowsiness, and shows definite ataxic movements of hands and feet. She has been taking orange juice and sugar at frequent intervals but not during the night. Since the beginning of her illness she has gained 46 pounds (20 kg.), apparently due to the increased food intake.

Essential Physical Findings. Height 5 feet 2½ inches (159 cm.), weight 186 pounds (80 kg.), pulse 80, temperature 98.6° F., blood pressure 140 systolic, 92 diastolic. The eyegrounds showed no abnormality, the visual fields were normal, pupillary reaction normal. The heart and lungs were negative both by physical and fluoroscopic examination. Abdominal examination revealed no abnormalities; the liver was apparently of normal size. There was marked rectocele and cystocele and the left ovary was slightly enlarged. The nervous reflexes, both deep and superficial, were normal throughout.

Laboratory Findings. Blood: hemoglobin, 96 per cent; red cells, 4,520,000; white cells, 8600; polymorphonuclears, 72 per cent; Kahn reaction, negative; blood sugar (before breakfast), 48.5 mg. per 100 cc. This was not, strictly speaking, a fasting blood sugar since only 6 hours had elapsed since taking sweetened orange juice. The estimation of the blood sugar throughout was by the Folin and Wu method. The urine was negative. Roentgen ray study of the long bones showed no abnormalities; the sella turcica was perhaps slightly smaller than average but otherwise normal.

Subsequent Studies. The patient was sent to Baylor Hospital for further observation. The blood sugar was estimated shortly after a convulsion and was found to be 35 mg. per 100 cc. Blood-sugar readings were made at 4-hour intervals over a period of 24 hours and ranged from 40 mg. to 55 mg. per 100 cc. The curve for the 24 hours is shown graphically in Fig. 1. Isolated blood sugars were estimated after intravenous glucose or meals and the highest reading obtained was 105 mg. Glucose tolerance test was not done on account of the danger of producing subsequent hypoglycemic shock. The blood cholesterol was 139 mg. per 100 cc. Basal metabolic

readings were not made on account of the impossibility of preparing the patient properly. If sugar in some form was not supplied at 3-hour intervals by day and night, she had some evidence of an impending seizure.

Therapy. An attempt was made to reduce the carbohydrate intake in the diet and at the same time to supply her with small amounts at regular intervals. So long as the total available glucose was in the neighborhood of 200 gm. in the 24 hours, she was free from trouble, provided not more than 3 hours elapsed between feedings. When, however, the total glucose was reduced to 150 gm., it was impossible to prevent the attacks.

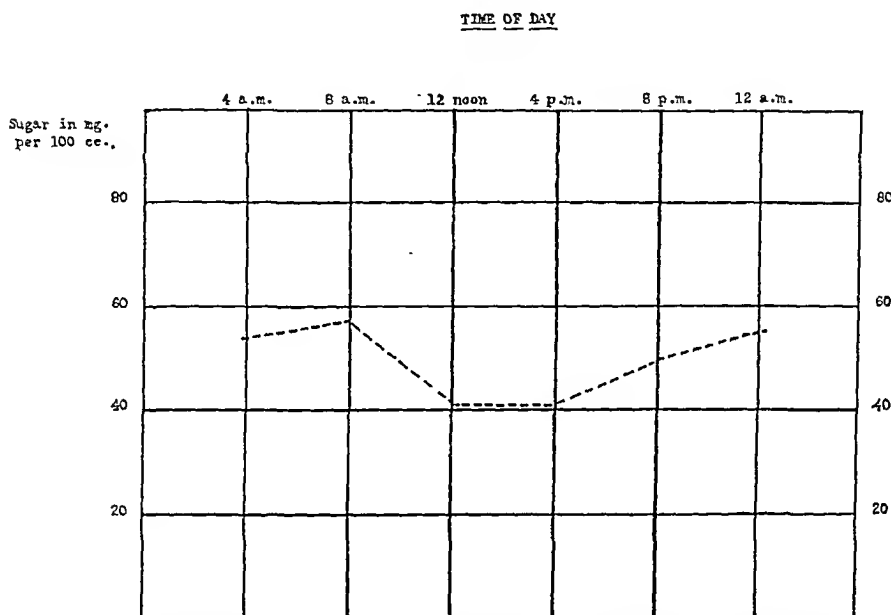


FIG. 1.—Blood-sugar curve for 24-hour period. The patient was receiving a total of 215 gm. of glucose in the diet during this period. The 8 A.M. reading is an interpolation from a previous day.

She was given thyroid steadily in the amount of 3 gr. (0.195 gm.) daily, without any appreciable effect upon her condition. Pituitary extract was given three times daily but proved to be of service only when administered in the presence of definite symptoms. Adrenalin was administered but once—this during a convulsion—and apparently had very little effect. It was not used more frequently for the reason that it was considered unwise to mobilize the glycogen reserve in the face of continued hypoglycemia.

Since medical treatment had little effect upon her condition, exploratory operation was decided upon. This was performed July 8, 1932, by Dr. W. E. Sistrunk. The pancreas was found to be about one-third normal size, being about 6 cm. in length and 2.5 cm. in width at the head. The tissue seemed friable but no evidence of a growth in the gland could be made out. A small piece of tissue was removed from the anterior central part of the body. No accessory pancreas could be discovered; the liver was apparently normal and nothing unusual was found in either kidney.

Dr. S. A. Wallace reported upon the tissue as follows: Specimen consisted of a small, red, friable portion of tissue, measuring 1 by 0.5 cm., cut with little resistance, was soft and slightly granular. Microscopic: Sections showed gland acini of normal size and appearance. The cells of the glands

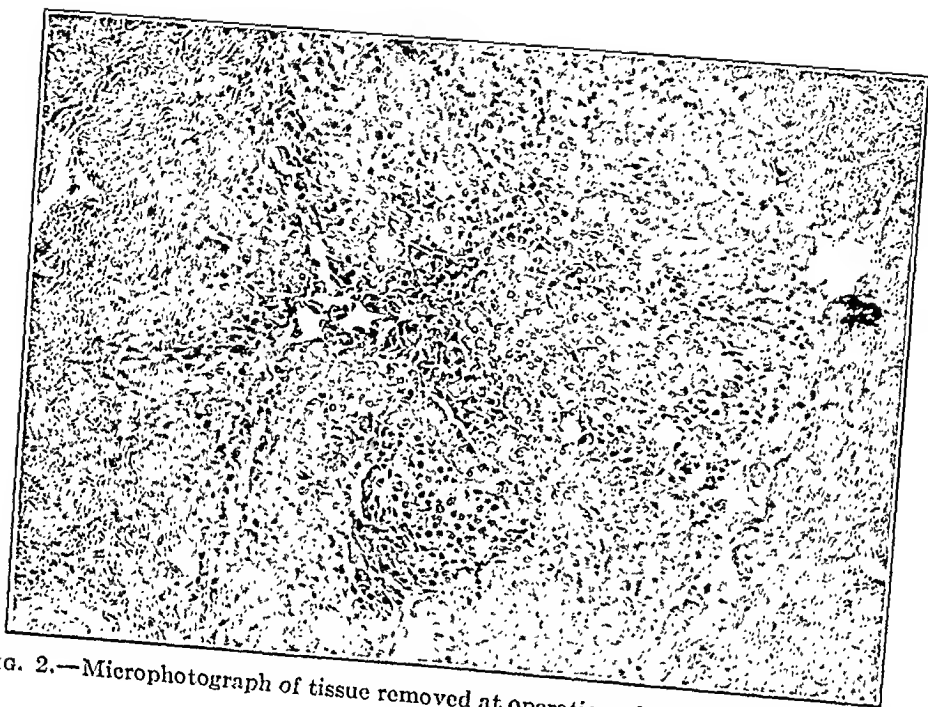


FIG. 2.—Microphotograph of tissue removed at operation, showing normal acini and islands.



were regularly arranged with uniformly round nuclei. The islands of Langerhans appeared normal in number and in general were slightly smaller than normal. The cells were not abnormal in appearance. Connective tissue trabeculae were slender. There were no malignant changes seen in sections examined. Diagnosis: Practically normal pancreatic tissue.

The microscopic sections were also examined by Dr. George T. Caldwell, who confirmed the above findings. The appearance of the section is shown in the photomicrograph.

Postoperative Course. The patient stood the operation very satisfactorily and had little trouble for the first few days. It was noticeable that she was hungry and began to eat much earlier than would be expected following an operation of this type. By observation it was possible to predict when an attack was imminent. She complained of headache, drowsiness, and at times nausea. There was distinct tremor even before the patient was aware of any disturbance. Sugar given at this point usually but not always prevented further trouble. On the other hand, the injection of 0.5 cc. of pituitary extract hypodermically produced prompt improvement which lasted usually 3 to 5 hours. The final schedule for her care was based upon a diet in which the starches and sweets were held at as low a level as possible so far as the three daily meals were concerned. Sweetened fruit juice was given between meals, at bedtime, and every 4 hours during the night. With the appearance of any symptoms such as headache, cough, nausea, somnolence, or tremor, pituitary extract, 0.5 cc., obstetrical strength, was given immediately. The use of pituitary extract is based upon the work of Burn,⁶ who found that the injection of this substance removed the symptoms of hypoglycemic convulsions and caused a rapid elevation of the blood sugar.

Discussion. This patient presented two symptoms which are not usually listed as those accompanying hypoglycemia. These were headache and cough. The relation of headache to other symptoms was constant. It was promptly relieved by the administration of sugar by mouth or glucose intravenously. In 1929 I reported a case of a man in whom headache developed regularly when the blood sugar fell to the low normal point of 73 mg.⁷ The cough also seemed to be a regular accompaniment of the fall in blood sugar and was likewise relieved by the administration of sugar or pituitary extract.

As regards the possible causes for this patient's condition, the following may be considered:

1. *Overproduction of insulin* due to increased intake of food, particularly carbohydrates. The effect of increased carbohydrate intake in producing increased glucose tolerance has been suggested by John,⁸ and Lennox⁹ has shown that there is a definite stimulation of the blood-sugar mechanism of the body following the intake of glucose. This patient, however, increased her glucose intake upon the advice of her physician, following the development of her trouble, and her gain in weight was subsequent to this.

2. *Hypoglycemia due to endocrine disturbance:* While it was not possible to obtain an estimation of the basal metabolic rate, there was nothing in this patient's condition to suggest that she suffered from hypothyroidism. Her configuration was not that usually found in pituitary obesity and indeed, aside from the fact that her periods were scanty, there was no basis for assuming that any

endocrinopathy apart from that involving the pancreas was present. The abdominal exploration included palpation of the kidneys and liver but nothing was found in connection with these organs.

3. *Tumor of the pancreas*, particularly adenoma, could not be excluded entirely. As Smith¹⁰ has noted, adenomas of the islands of Langerhans are fairly frequent but may be difficult to detect except by minute study. If such was present in this case, however, there was nothing to indicate it.

4. *Disturbance in the balance between the external and internal secretion of the pancreas*: There is evidence that a relationship exists between the external and internal secretions of the pancreas. Lueders and Watson¹¹ were able to show that the injection of insulin in patients with malnutrition produced a measurable increase in the concentration of pancreatic ferment recovered from the duodenum. Bensley,¹² in 1911, demonstrated hypertrophy of the islets together with degeneration of the acini after obliteration of the duct, and Mansfeld¹³ found an increased sugar tolerance in dogs following ligation of the body of the pancreas. De Takáts *et al.*¹⁴ found an increased sugar tolerance following division of the pancreas with electric cautery. They were unable to say whether the stimulation of the operation resulted in hypertrophy and hyperplasia of the islet tissue, whether there was an increase in insulin output, a change in the secretory rate as a result of change in innervation, or a functional liver block with diminished output of glycogen.

Terbrüggen and Heinlein¹⁵ exposed the pancreas in rabbits to strong Roentgen ray treatment after isolating it and protecting surrounding organs. The rabbits died from hypoglycemic shock after 7 to 10 days. The pancreas showed degeneration of the excretory cells with little or no effect upon the islets. Since hypertrophy or hyperplasia of the islet tissue is not universally demonstrable following ligation of the pancreas or exposure to Roentgen ray, it seems possible that other factors may be concerned. Epstein and Rosenthal¹⁶ found that the passage of trypsin into the blood stream of the pancreas neutralizes insulin and by passing into the portal circulation causes glycogenolysis with a consequent hyperglycemia. They concluded that no definite barrier exists between the structures which produce internal secretion and those concerned with the external secretion of the pancreas. They indicate the possibility that the internal flow of trypsin may be a part of the mechanism which regulates the supply and activity of the internal secretion of the pancreas. They also concluded that inactivation of insulin by trypsin may occur within the body of an animal under suitable conditions. This work has been confirmed by La Barre and Booleman,¹⁷ who found that the products of acinar secretion, and particularly protrypsin in the blood supply of the islets, produces almost complete inactivation of insulin. It is a recognized fact that a relatively small amount of normal islet tissue may provide sufficient insulin for sugar metabolism. The idea may be advanced that the

small pancreas in this patient contained sufficient tissue capable of secreting a relatively normal amount of insulin. If ligation of the pancreas, obstruction of the duct, or other disturbances which cause atrophy of the acini may be assumed to act in some instances, by removing the inhibiting effect of acinar secretion it seems possible that the reduced amount of externally secreting tissue may have failed to provide an inhibiting effect upon the insulin. If this hypothesis is adopted, it is not necessary to assume that there was either overproduction of insulin (hyperinsulinism) or the release of abnormal insulin (dysinsulinism) in this case.

Concerning the use of the term hypoplasia, it must be admitted that this is not frequently encountered as regards the pancreas. In a personal communication Opie says: "There is no doubt, I think, that hypoplasia of the pancreas occurs and may affect the pancreas as a whole. . . . I assume that the term hypoplasia is applicable to a congenital condition in which one or all of the elements of the organ, although otherwise normal, are of abnormally small size or number." This term is applied to other organs which are below normal in size but in which the cellular structure is normal, hence there would seem to be no objection to its use in this case. The microscopic study of the section showed no evidence of cell degeneration or of fibrous replacement of tissue. Furthermore, since atrophy of the pancreas is frequently accompanied by diabetes, this would seem an argument against applying the term atrophy to the condition encountered in this patient.

Summary. A patient presenting convulsions together with a typical syndrome of hypoglycemia is reported. In addition, she showed two symptoms not usually included in the syndrome, namely, headache and cough. There was evidently hypoplasia of the pancreas. It is suggested that the hypoglycemia may be due to a disturbance between the internal and external secretion of the pancreas with a loss of the inhibiting effect of trypsin upon insulin.

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THE USE OF EPHEDRIN DURING SPINAL ANESTHESIA FOR THE RELIEF OF PARALYTIC ILEUS.

A THERAPEUTIC FALLACY.

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THE popularization of spinal anesthesia for the operative manipulation of somatic sensory areas has allowed the surgeon, without trepidation, to extend the usefulness of this procedure to the relief of paralytic ileus.^{1,2,3} In the latter condition there is a complete cessation of intestinal motility, unassociated with mechanical obstruction and arising reflexly from some intraabdominal condition. As demonstrated by Markowitz and Campbell,⁴ the nature of paralytic ileus and the rationale of its relief through the employment of spinal anesthesia can be understood by a consideration of the scheme of sympathetic reflexes through the spinal cord. In Fig. 1 there is diagrammed the sympathetic reflex arc made up of an afferent fiber (*A*) which conveys sensory impulses from the abdominal parietes, an intercalated or connecting neuron (*B*) lying within the spinal cord, and an efferent fiber (*C*) which, being sympathetic in origin, will on stimulation lead to an inhibition of intestinal motility and to splanchnic vasoconstriction, the latter increasing the blood pressure. Under normal conditions, there being no potent stimulation of the sensory nerve endings in the parietes, there is no great inhibition of intestinal motility from this source. If, however, the peritoneum becomes inflamed or there is sensory stimulation of (*A*) by such an agency as a renal calculus or twisted ovarian cyst, a stream of impulses ascends the sensory fiber to set up a reflex stimulation of the motor path inhibitory to intestinal motility.

The treatment of paralytic ileus by spinal anesthesia aims to break up the integrity of the reflex arc at the intercalated neuron. As soon as the communication between the sensory and motor fiber becomes disrupted, intestinal contractions resume under the

influence of the vagus. At the same time, however, there is a fall in blood pressure due to the removal of the tonic vasoconstricting impulses which ordinarily flow through the sympathetic motor fiber.

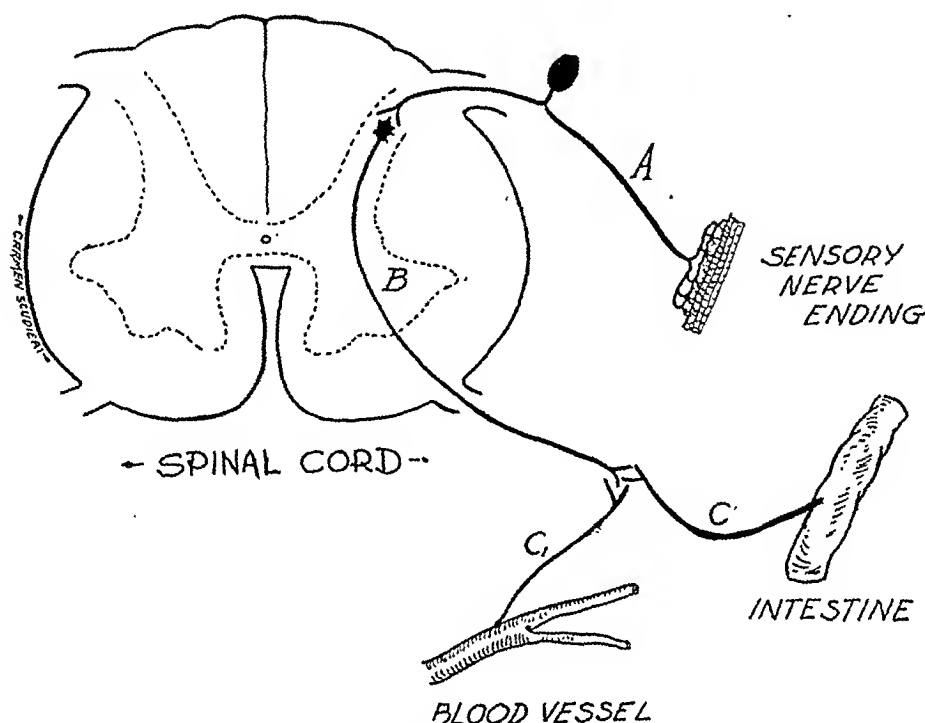


FIG. 1.—Diagrammatic representation of visceral reflex arc in thoracolumbar nervous system.

To counteract the hypotension accompanying spinal anesthesia, ephedrin is ordinarily used. The action of this drug is comparable to that of epinephrin in that it exercises its pressor effect by stim-

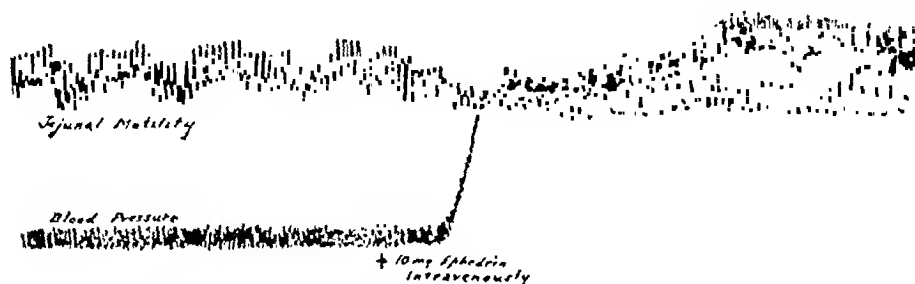


FIG. 2.—Effect of intravenously administered ephedrin on blood pressure and intestinal motility under spinal anesthesia.

ulation of the sympathetic myoneural junction. Since the inhibitory nerve endings in the intestinal wall are also sympathetic in origin, there is reason for assuming that ephedrin will inhibit intes-

tinal motility even during the course of spinal anesthesia. We therefore decided to determine experimentally whether such was actually the case.

Experimental.—Dogs under ether anesthesia were prepared for continuous tracings of blood pressure and intestinal movements. A three-way paraffined glass cannula was inserted into the carotid artery and connected with a citrate pressure bottle and a mercury manometer. An air-filled rubber balloon was inserted into the jejunum and connected with a chloroform manometer. After an adequate control record of blood pressure and intestinal motility had been secured, the dog was placed on its side, and 0.5 cc. of spinocain was administered intraspinaly. The dog was then replaced upon its back, the head slightly lowered. After results were secured from this procedure, 10 mg. of ephedrin sulphate were given either subcutaneously or intravenously, and the effects noted.

Results.—In the 4 animals studied there was an absence of intestinal motility at the initiation of the experiment, presumably due to the peritoneal irritation attendant on opening the abdominal wall and the insertion and presence of the jejunal balloon. About 10 minutes after the introduction of spinocain, intestinal motility returned concurrently with a gradual fall in blood pressure. The administration of ephedrin caused a resumption of the original blood pressure level and an immediate cessation of intestinal motility (Fig. 2).

From the above results we believe the use of ephedrin as a pressor substance in spinal anesthesia, where the latter is initiated for the relief of paralytic ileus, to be contraindicated. These results are in harmony with the theoretical considerations which may also be advanced. It would seem logical that in the use of spinal anesthesia for this particular purpose, the use of ephedrin be dispensed with and, if the fall in blood pressure becomes alarming, recourse be had to some other method of maintaining it, such as the administration of physiological saline.

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ON THE ALLEGED ANTAGONISM BETWEEN DIGITALIS
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THE use of digitalis in the treatment of cardiac disorders occurring in diphtheria has been the subject of clinical controversy. The combined effects of digitalis and diphtheria toxin have also been investigated experimentally. Prejudice against the use of this drug in heart disease due to diphtheria has arisen mainly from the fact that the electrocardiographic changes resulting from diphtheria are similar in many respects to the effects of digitalis poisoning.¹ Haskell² found that a single dose of digitalis did not prolong the life of guinea pigs poisoned by diphtheria toxin, and obtained some indication that very large doses of digitalis were injurious. Edmunds and Cooper³ found that the injection of digitalis into dogs severely poisoned by diphtheria toxin resulted in improvement of the circulation in acute experiments, although these dogs were more susceptible to digitalis than normal animals. In similar experiments on the cat Gold⁴ found that even though diphtheria toxin had produced severe pathologic changes in the heart, the minimal average fatal dose of digitalis was the same as that for normal animals, but when the animals became moribund a marked increase in their susceptibility to digitalis appeared. These experiments confirmed the observation of Edmunds and Cooper that digitalis may stimulate the damaged circulation in poisoning by diphtheria toxin, and also served to explain the increased susceptibility to the toxin that was found in their dogs.

Recently there appeared a paper by Myers⁵ in which the results of experiments on large numbers of guinea pigs seem to show a very striking protective action of digitalis against poisoning by diphtheria toxin. The author stated that the daily subcutaneous injection of digitalis for several days before or after the injection of the diphtheria toxin, protected guinea pigs almost completely against more than the fatal dose of the toxin, so that the animals failed to show symptoms of poisoning by the toxin and failed to develop the pathologic changes in the heart seen in animals that received the toxin alone. These results are exceedingly interesting because they attribute to digitalis a new action which has not hitherto been de-

scribed and which is apart from its action on the circulation, namely, that of a chemical antagonist to diphtheria toxin. Although Myers went far afield in stressing the application of these results to the toxemia of pneumonia in man, they would still be of considerable practical significance if they were applicable to diphtheria in man. It would not be possible to digitalize man or the cat without serious poisoning by the plan of dosage employed by Myers in guinea pigs, but the author attached great importance to such a plan of dosage in order to obtain the protective action of digitalis against the diphtheria toxin. In view of the striking results obtained by Myers, it was deemed desirable to investigate this matter in the cat, an animal which vomits from digitalis (the guinea pig does not vomit), and which in other respects has been shown to behave more like man in response to the digitalis bodies than do rodents. The results of this investigation form the subject of the present report.

Experimental. Experiments were carried out on a series of 66 cats. The analysis is based on the results obtained in 59 animals only, the others having been used for preliminary tests of the toxin or discarded because of infection or of abnormal behavior in the early part of the experiments. Of the remaining ones 29 received the toxin alone and served as controls for the other 30 which received the toxin in addition to digitalis for varying periods of time and in various doses.

The animals were kept in separate cages in a large room provided with ample sunlight and air. They were fed a diet of meat and water. Milk was sometimes used for testing the appetite, but was discontinued because it produced diarrhea. It was found that when the animals began to refuse meat, they usually also refused the milk. The animals were weighed daily and observations were made of the course of the poisoning. Postmortem examinations, especially for gross pathologic changes in the heart, were made in most of the animals.

A 4-ounce specimen of aged diphtheria toxin (undiluted) was obtained from the Department of Health of New York City on March 22, 1932. The last injection of this toxin was made on May 25, 1932. The specimen was kept on ice and from it a few cubic centimeters were taken when necessary for dilution, so that the original specimen was never removed from the ice chest for more than a few moments, nor was it exposed to the light. Fresh solutions were made up immediately before the injections in the case of each series. The toxin was injected intravenously in all except a few instances in which subcutaneous injections were given, and in most cases in dilutions of 1 to 100 or 1 to 200. The fact that in most instances a control group of cats received the same dose of diphtheria toxin of the same diluted specimen and at the same time as a digitalis series, served as a check on any possible deterioration of the toxin during the course of the investigation.

The effects of the diphtheria toxin were fairly uniform in most cases. After doses of 0.002 cc. of our specimen of toxin per kilogram,* the appetite was often found impaired by the second or third day; by the fourth or fifth day the animal frequently refused food completely, and a day or two before death it usually refused water as well. During the course of the poisoning there was sluggishness, drowsiness, weakness, nausea and vomiting, diarrhea (not due to milk), muscle twitching, partial paralysis usually of the hind limbs, although in a few cats also of the fore limbs, extreme weakness, prostration and death. In many cases death was attended by a convulsion and cessation of the heart in a manner that appeared similar to the effects of a rapid intravenous injection of digitalis. After 6 or 7 days in which the animal appeared ill, though still in fairly good condition, prostration frequently developed very rapidly, leading to death within a few hours or a day. The dose of 0.002 cc. caused death in all of 13 control animals on from the 5th to the 13th day. Larger doses of the toxin up to 0.1 cc. caused similar symptoms which came on much more rapidly. The duration of life after the administration of toxin varied from less than 18 hours to about 550 hours, depending on the dosage which ranged in these experiments between 0.1 and 0.001 cc.

The standard minimal lethal dose for guinea pigs (death of 250-gm. guinea pigs on the 4th day) of this specimen of toxin was 0.002 cc. This would be equivalent to 0.008 cc. per kg. Such doses caused death in cats in about 2 to 3 days (Table 2). In most of our experiments, however, we employed doses nearer to the absolute minimal fatal dose with the view of bringing out more strikingly any antagonism that might obtain between the toxin and the digitalis. It was not deemed feasible to use any smaller doses than 0.002 even though 0.001 cc. caused death (in 552 hours) because of possible complicating factors that might be introduced by excessively prolonged starvation. A dose of 0.0005 cc. was survived. After this dose anorexia and weakness appeared by the 5th day, but by the 8th day the animal began to improve and gain weight.

A tincture of digitalis, which was in use in a large cardiac clinic, and which proved to be very satisfactory clinically, was employed throughout this study. Its potency determined by one of us (H. G.) was 0.9 per cat unit. This was regarded as the average fatal dose. It was administered intravenously and in one group by stomach tube in varying percentages of this dose per kilogram of body weight.

Results. The results have been summarized in Tables 1 to 4, which compare the survival periods of the cats which had received injections of the diphtheria toxin alone with those which had received digitalis as well.

* All doses of toxin and digitalis were given per kilogram of body weight. Hence, for the sake of brevity, "per kilogram" will not be repeated.

In the first series of 11 animals (Table 1) the dose of toxin was 0.01 cc. (except in 2 of 6 controls which received 0.02 and 0.1 cc., respectively). Five of these received 1 large dose of digitalis (25 to 50 per cent of the average fatal dose) intravenously from 1 to 2 hours before the toxin. The digitalis caused vomiting in all but No. 7, 1 of the 2 which received the smaller dose of digitalis. All 11 animals died in about the same length of time.

TABLE 1.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Digitalis (per cent cat unit per kg., intravenously).
1	0.10	2 to 18	0
2	0.02	2 to 18	0
3	0.01	2 to 18	0
4	0.01	30 to 46	0
5	0.01	30 to 46	0
6	0.01	25	0
7	0.01	23	25
8	0.01	23	25
9	0.01	3 to 18	50
10	0.01	24	50
11	0.01	29 to 45	50

Animals No. 7 and No. 8 received the digitalis 2 hours before the toxin; Nos. 9 to 11, 1 hour before the toxin. The survival periods are stated in 2 numbers in cases in which the animal was found dead on the following morning, the first figure showing the period during which the animal was known to have been alive and the second the total interval up to the time it was found dead.

TABLE 2.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Degree of cardiac pathology.	Digitalis (per cent cat unit per kg., intravenously).
1	0.008*	48	...	0
2	0.008*	78 to 94	...	0
3	0.006*	29 to 45	...	0
4	0.005	41	...	0
5	0.005	45	++++	0
6	0.005	45	++++	0
7	0.005	50 to 66	++++	0
8	0.005	29 to 45	+++	66
9	0.005	29 to 45	++++	25 + 25
10	0.005	45	++++	25 + 25

* These 3 are the only cases in which the toxin was injected subcutaneously.

In a second series of 10 animals (Table 2) a longer period elapsed after the administration of digitalis before the toxin was given, and a smaller dose of the toxin was used, 0.005 cc. in all except in 3 of the 7 controls. To 1 animal (No. 8) 66 per cent of the average fatal dose of digitalis was given intravenously 2 days before the toxin. This induced vomiting. Each of 2 others (Nos. 9 and 10) received 25 per cent of the average fatal dose of digitalis intravenously on each of 2 successive days. The second dose caused vomiting in 1 of these (No. 10). The toxin was administered on the day follow-

ing the second dose of digitalis. None of the 3 animals had shown any toxic signs of digitalis action when the diphtheria toxin was injected. All 10 animals showed similar symptoms of diphtheria poisoning, and all died. Those receiving digitalis did not live any longer than the controls, and the gross pathologic changes in the hearts were indistinguishable in the two groups.

In a third series of 6 animals (Table 3) a still smaller dose of diphtheria toxin was given, 0.003 cc., and larger doses of digitalis were given intravenously in fractions at intervals of several hours before the toxin. No. 4 received 4 doses of 25 per cent of the average fatal dose each, 29, 5, 4 and 3 hours, respectively, before the toxin. No. 5 received 3 doses of digitalis of 50, 25 and 25 per cent of the average fatal dose, 5, 4 and 3 hours, respectively, before the toxin. No. 6 received 2 doses of digitalis of 50 and 25 per cent of the average fatal dose, 5 and 4 hours, respectively, before the toxin. In all 3 vomiting was produced by digitalis, the first 2 having been tolerant animals, because emesis did not occur until after an average fatal dose. All 6 of this series of animals developed typical symptoms of diphtheria poisoning, and all died. Those receiving the very large doses of digitalis died somewhat sooner than the controls. Such large doses of digitalis were not used again because of the possibility that they themselves might cause death.

TABLE 3.

Animal No.	Dose of diphtheria toxin, cc. per kg.	Duration of life, hours.	Digitalis (per cent cat unit per kg., intravenously).
1	0.003	146 to 162	0
2	0.003	121 to 137	0
3	0.003	146 to 162	0
4	0.003	73 to 91	25 + 25 + 25 + 25
5	0.003	26	50 + 25 + 25
6	0.003	164 to 180	50 + 25

It is generally accepted that one large dose of digitalis exerts essentially the same cardiac actions as the same intensity of digitalization with smaller doses over a long period of time. Large doses given for a short time before the toxin in our experiments were without antagonism to diphtheria toxin, and since Myers stressed the importance of prolonged treatment with digitalis in his guinea pigs, in order to elicit the antagonism we carried out the largest series of experiments in cats with more prolonged digitalis administration. In these, also the smallest dose of toxin was used. Each of 32 cats received 0.002 cc. toxin (Table 4) and of these 13 (Nos. 1 to 13) served as controls while 19 received digitalis for varying periods of time before and after the toxin. The exact dosage and intervals were not the same in every case because it was aimed to maintain a state of full digitalization by small daily doses.

When sufficient cumulation occurred in any case to cause loss of appetite or vomiting, the dose was withheld for 1 or 2 days and then its administration was resumed. When the animal became ill from

TABLE 4.—SHOWING EFFECT OF PROLONGED DIGITALIZATION IN ANIMALS RECEIVING SMALLEST DOSE OF DIPHTHERIA TOXIN, 0.002 CC. PER KG.

Animal No.	Duration of life, hours.	Degree of cardiac pathologic change.	Digitalis dosage (per cent cat unit per kg. daily).
1 . . .	218	+?	0
2 . . .	149 to 163	+++	0
3 . . .	195 to 211	—	0
4 . . .	196 to 212	+?	0
5 . . .	217	+++	0
6 . . .	144 to 160	++	0
7 . . .	217 to 233	+?	0
8 . . .	314 to 330	+?	0
9 . . .	172	++++	0
10 . . .	189	++	0
11 . . .	100 to 116	+?	0
12 . . .	168 to 184	+++	0
13 . . .	100 to 116	++++	0
<hr/>			
14 . . .	144 to 160	++	50, 0, T
15 . . .	96 to 112	+?	50, 0, T-20
16 . . .	45	++	50, 0, T-20
17 . . .	94	+?	50, 0, T-20
18 . . .	198 to 214	+?	25, T-20, 0, 0, 0, 0, 10, 0, 0, 10
19 . . .	198 to 214	++	25, 0, T-20, 0, 0, 0, 0, 10, 0, 0, 10
20 . . .	264 to 280	+++	25, 0, T-20, 0, 0, 0, 0, 10, 0, 0, 10
21 . . .	212	++	25, 0, T, 0, 0, 0, 0, 10, 0, 0, 10
22 . . .	168 to 184	+?	25, 0, T-20, 0, 0, 0, 0, 10
23 . . .	116 to 232	++++	20, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 20
24 . . .	310 to 312	+?	10, 10, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 0, 20, 0, 0, 0, 10
25 . . .	312 to 328	+?	10, 10, 10, 10, 10, 0, 10, 10, 0, 10, T-30, 0, 0, 0, 0, 20, 0, 0, 0, 10
26 . . .	168 to 186	++++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 0, 0, 0, 0, 10, 10
27 . . .	69	++++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10
28 . . .	96 to 114	+++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10
29 . . .	96 to 114	+	20, 20, 0, 5, 0, 10, 10, T-10, 10
30 . . .	48 to 66	++	20, 20, 0, 5, 0, 10, 10, T-10, 10
31 . . .	192	+++	20, 20, 0, 5, 0, 10, 10, T-10, 10, 0, 0, 0, 0, 10, 10
32 . . .	192 to 208	++	20, 20, 10, 10, 0, 5, 0, 10, 10, T-10, 10, 0, 0, 0, 0, 10, 10

The digitalis was injected intravenously in all cases except in Nos. 26 to 32, to which the drug was given by stomach tube.

See Table 1, footnote, for the significance of the 2 numbers under the "Duration of Life."

The line of figures under "Digitalis Dosage" lists the doses of digitalis given on consecutive days from the beginning of the experiment up to the last injection. "T" represents "toxin," and the figure after it, the dose of digitalis given on the same day.

Under the "Degree of Cardiac Pathologic Change" are listed estimates of the amount of gross cardiac damage as indicated in most cases by the size and number of gross hemorrhages in the heart.

the diphtheria toxin it frequently vomited, and this was difficult to distinguish from digitalis overdosage. In some of these cases the digitalis was withheld for a few days in order to avoid the danger of killing the animal with digitalis. In most instances vomiting had occurred from digitalis before the toxin was administered. In no instance was the animal appreciably depressed from the digitalis before the toxin was given.

The experiments in this series fall into four groups: The first group (Nos. 14 to 17) received 1 large dose of digitalis 2 days before the toxin and a smaller dose on the day the toxin was given (except in No. 14 in which there was still some anorexia 2 days after the first dose of digitalis). Most animals of the second group (Nos. 18 to 22) received 1 large dose of digitalis 2 days before the toxin, a smaller dose on the day of the toxin administration, and in all but 1 case 2 smaller doses subsequently. The animals of the third group (Nos. 23 to 25) received digitalis during a period of 9 to 10 days up to the day on which the toxin was injected, at which time an additional 30 per cent of the fatal dose was given to insure full digitalization. One or 2 additional doses of digitalis were given during the course of the diphtheria poisoning after a sufficient interruption to insure that the animal would not be suffering from digitalis poisoning. In all of the above 3 groups the digitalis was given intravenously. In the 4th group (Nos. 26 to 32) it was given by stomach tube, the figures in Table 4 indicating percentages of the intravenous average fatal dose. These animals received digitalis up to the point of anorexia, nausea or vomiting during a period of 7 to 9 days prior to the toxin injection and then from 2 to 4 additional maintenance doses of digitalis during the course of the poisoning by diphtheria toxin.

An examination of the survival periods and the degree of gross pathology in the heart in the 13 control animals of this series and the 19 treated with digitalis by these various methods shows no evidence of antagonism. Not one of the digitalized cats lived longer than the longest survival period of the controls, while several of the cats receiving very large doses of digitalis showed survival periods much shorter than the shortest periods of the controls. It appears, therefore, that very large doses of digitalis hastened their death.

Most of the hearts showed numerous areas of hemorrhage in the mural pericardium and endocardium, varying in size from that of a pinhead to about 0.25 cm. in diameter. As seen in Table 4, these were similar in the controls and treated animals.

Comment. As we have already mentioned, the present study on the cat was suggested by the very striking results obtained in guinea pigs by Myers, working in Dixon's laboratory in Cambridge. These results seemed to show practically complete protective action

by digitalis against fatal doses of diphtheria toxin in guinea pigs. Our results with 59 cats show, on the contrary, that digitalis does not protect this animal in the slightest degree against diphtheria toxin, and that very large doses hasten its death.

Myers appears to have been interested in the problem of digitalis in pneumonia. He spoke of the lack of general agreement as to the value of digitalis in pneumonia, and cited among other papers several statistical studies of war data which recommended the use of digitalis, but made no reference to the only systematic and controlled statistical studies of this subject in large groups of patients that had ever been made, namely, those of the Pneumonia Committee⁶ of Bellevue Hospital in New York City, which included an intensively studied series of about 1000 patients and covered a period of nearly 3 years. The data obtained in these studies leave little doubt that the routine use of digitalis in pneumonia does not lessen the mortality and give some indication that it may increase it. Myers stated: "The primary object in devising and carrying out this investigation was to determine whether in acute pneumonia digitalis could be regarded as a life-saving remedy, and to this I think I give a clear answer in the affirmative." It is well to bear in mind that this conclusion is based not upon observations with a "toxin" of pneumonia in patients, but with the toxin of diphtheria in guinea pigs, and that our experiments have shown that in the cat—an animal which behaves more like man in response to the digitalis bodies—digitalis exerts no protective action against diphtheria toxin.

Summary. Our results show that digitalis does not afford any protection against poisoning by diphtheria toxin in the cat. It is probable that the same is true in man. Results obtained with diphtheria toxin in guinea pigs had been used as a basis for the statement that "in acute pneumonia digitalis could be regarded as a life-saving remedy." This assumption is unwarranted and has received no support from systematic statistical studies which show that the routine use of digitalis in pneumonia does not lessen the mortality.

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ACUTE ANGIOSPASTIC RETINITIS: OCCURRENCE IN CASES OF SEVERE HYPERTENSIVE AND RENAL DISEASE.*

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ALTHOUGH the clinical distinction between chronic glomerulonephritis and diffuse vascular disease such as malignant hypertension is usually definite, cases are occasionally seen which present some of the characteristics of both conditions. Also, in a given case observed at different times the preponderance of evidence of diffuse vascular or renal pathologic processes may change a good deal as the disease progresses. The appearance of the ocular fundi is frequently a very important aid in the distinction between the two conditions, although this picture also may change considerably with the development of the disease.

In the course of cardiovascular renal disease 3 types of retinitis occur which present sufficiently characteristic ophthalmoscopic appearances to permit of rather accurate diagnosis of their etiology. The retinitis of severe essential hypertension, the retinitis of malignant hypertension and the retinitis of chronic glomerulonephritis have features which enable the observer to distinguish them readily in most instances. In a certain number of cases a form of retinitis occurs which is not typical of any of these 3 groups, and which is best classified ophthalmoscopically under the general term of acute angiospastic retinitis.

The diffuse or localized edema, the flame-shaped or round hemorrhagic areas and the cottonwool patches which appear as acute processes in the retina in the course of the various types of cardiovascular renal disease are probably of angiospastic origin. The punctate hemorrhages and areas of degeneration which are based on organic occlusion of arterioles or capillaries are apparently of more gradual onset, and of more chronically progressive course and are usually localized to single areas of the retina (retinitis of arteriosclerosis). Lesions based on organic closure of retinal veins or larger arteries are likely to be of sudden onset, but they present aspects readily distinguished from those of diffuse retinitis.

* Submitted for publication, June 20, 1932.

In the average case of severe hypertensive disease a tendency to recurrent relatively localized angiospasm is manifested by the appearance in the retina from time to time of scattered cottonwool patches and hemorrhagic areas. In such cases sclerosis of the arterioles is always present. In the more fulminating types of hypertension, diffuse retinitis, with edema of the disks, is frequently seen. This type of retinitis also is usually engrafted on visible sclerosis of the arterioles. In acute or subacute glomerulonephritis angiospastic retinitis can occur which is similar to that of severe benign hypertension except for the normal appearance of the walls of the arterioles. In the terminal phases of chronic glomerulonephritis diffuse retinitis occurs when arterioles have previously been normal, and is often angiospastic. Acute angiospastic retinitis without visible arteriolosclerosis or localized angiospasm, although it always occurs in association with elevated blood pressure, is then not characteristic of primary hypertensive disease, but from the ophthalmoscopic standpoint alone is always more suggestive of primary diffuse glomerulonephritis. It has been demonstrated to occur, however, when the primary condition, as proved by the other clinical and laboratory manifestations and by the subsequent course of the disease, is a diffuse disease of the arterioles throughout the body.

The characteristics of acute, diffuse angiospastic retinitis are generalized, marked attenuation of the retinal arterioles with or without irregularity of their lumina, diffuse edema of the retina, relative ischemia at times, with mild edema of the disks, cottonwool patches, hemorrhagic areas and, in the later stages, punctate exudates of residual edema and partial star figures in the macular regions. In most cases it is impossible to determine that actual or organic disease of the walls of the arterioles is present. The arterioles in these cases do not show the exaggerated reflex and definite, sharply defined indentation of the walls characteristic of the slowly developing sclerosis of hypertension, and arteriovenous compression is not present. The points of excessive narrowing of caliber are irregularly distributed, are of varying extent and usually are marked by some haziness of the perivascular retina. In a few cases recent or organized thrombi have been seen in small arterioles, and have been considered by us as strong evidence of active disease of the intima. Such findings in the retina denote diffuse disease of the arterioles. The type of acute angiospastic retinitis here described among men and nonpregnant women is essentially similar to the retinitis seen in toxemia of pregnancy. If the patient lives beyond the acute stage of the disease the retinitis may have one of several outcomes. It may heal completely, leaving only the signs of past retinitis, mild pallor of the disks with increased connective tissue, residual perivascular thickening and perhaps mild pigmentary proliferative changes in the retina and choroid. It may result in

chronic obliterative disease of the arterioles, retinitis of arteriolosclerosis. It may gradually assume the characteristics of malignant hypertension (Group 4 as described by Keith), with definite sclerosis of the arterioles and gradually increasing edema of the disks. The course of the retinitis is often but not invariably indicative of the course of the general disease. If the retinitis ends in complete healing the primary disease probably has been glomerulonephritis, and the patient may recover or go on to chronic glomerulonephritis. If the retinitis develops into the arteriolosclerotic type hypertension of the severe essential type is the usual outcome. If the retinitis assumes the malignant type the patient will have rapidly progressive hypertensive disease.

Case Reports. CASE 1.—A man, aged 38 years, was admitted to the Mayo Clinic April 11, 1929, complaining of severe, continuous frontal headaches of 9 weeks' duration. They were relieved by lying down and aggravated by rising. He had had scotomata since the onset of headaches. For 6 weeks previous to admission he had noticed some impairment of vision. He complained, also, of urinating once or twice at night. He had had slight dyspnea for about a year. For 6 or 8 years he had noticed some puffiness of the eyelids at intervals.

Vision was 6/60 in each eye. The pupils, reflexes, and peripheral visual fields were normal. Ophthalmoscopic examination revealed acute angiospastic retinitis, without any definite sclerosis of the arterioles. Venous stasis was marked, and considerable edema and hemorrhagic extravasations were present in the retina. The tonsils appeared to be infected. The lungs were normal. The area of cardiac dullness extended 3 cm. to the right and 10.5 cm. to the left of the midsternal line; a systolic murmur was heard at the apex and at the base; the second sound at the aortic area was accentuated, graded 1. There was peripheral sclerosis, graded 2. The blood pressure in millimeters of mercury was 210 systolic and 125 diastolic. The liver was palpable.

Laboratory Tests. The specific gravity of the urine was 1.010, albumin was graded 3, there was no sugar, erythrocytes were graded 3 on one occasion, and on the same occasion a few pus cells were seen. Excretion of phenolsulphonephthalein after intravenous injection was 40 per cent in 1 hour. In the dilution test the lowest urinary specific gravity was 1.002. *Blood:* Hemoglobin, 18.7 gm. per 100 cc.; erythrocytes, 4,400,000, and leukocytes 5000 per c.mm.; urea, 86 mg. per 100 cc. (this was reduced to 53 mg. by the time of dismissal) creatinin 3 mg. per 100 cc.; CO₂ combining power 68 vol. per cent; chlorids 618 mg. per 100 cc. A serologic test of the blood for syphilis was negative. An electrocardiogram showed left ventricular preponderance.

Histologic study of the arterioles in a small piece of pectoralis major muscle removed for biopsy revealed definite but rather inconstant changes. The average ratio of wall to lumen was 1 to 1.6, but individual ratios varied from 1 to 0.9 to 1 to 2 (normal 1 to 1.7 to 1 to 2.7). The maximal changes were noted in arterioles from 50 to 100 micra in diameter. The nuclei of the cells in the media of the arterioles were more than normally numerous; the intimal nuclei appeared normal. There was moderate tortuosity.

Three weeks following admission of the patient there were definite macular stars in the ocular fundi and moderate arteriolosclerosis of postretinitic type. The retinitis simulated that of glomerulonephritis in its character and course, because of the absence of definite sclerosis of the arterioles. The marked variations in ratio of wall to lumen of the various arterioles

seen in the specimen of muscle removed for biopsy suggested that only part of the arteriolar bed had suffered organic injury, but that the disease was quite widespread. In spite of the condition of the retina, the clinical picture suggested hypertension rather than renal disease.

A diagnosis was made of early malignant hypertension, arteriolosclerosis and tonsillar sepsis. We learned that this patient died February 1, 1930.

CASE 2.—A man, aged 31 years, was admitted to the clinic October 27, 1930, complaining of blood in his urine and swelling of his ankles. In April, 1930, he had had a sore throat for a day. Two weeks later he noticed blood in his urine which persisted for several days. May 20, some edema developed involving the face, ankles, and lower part of the back; on several occasions he vomited. On the advice of his physician he remained in bed for 3 weeks on a diet low in protein and salt. Following this, the edema was much decreased, but it had increased slightly afterward, which was noticeable when he was up and about. July 27, tonsillectomy had been performed. For 9 weeks ~~continued~~ ^{continued} in bed. During this time his physician ~~and~~ ^{and} elevation of blood pressure. In addition, occipital headaches were occasionally present. When ambulatory, there was occasionally frequency of urination. Two years previous to his admission his blood pressure was found to be elevated in the course of an examination for insurance. He had no subjective disturbance of vision.

The patient's face was puffy and pale. Vision was 6/4 in each eye. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed acute angiospastic retinitis, with evidence of commencing resolution. The retinal arterioles showed marked attenuation but sclerosis was not definitely visible. The peripapillary retina was mildly edematous and cottonwool patches and hemorrhagic areas were present. All these changes were more marked in the left eye in which there was also a partial macular star. The lungs appeared to be normal. The area of cardiac dullness extended 2 cm. to the right and 14 cm. to the left of the median line, the heart tones were clear, there were no murmurs, and the aortic second sound was accentuated, graded 1. Peripheral sclerosis was graded 1. The blood pressure, studied over a period of 24 hours, showed a systolic range of 150 to 210 and a diastolic range of 90 to 150 mm. mercury. Edema of the thoracolumbar region was graded 1, and of the ankles graded 1.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 3, there was no sugar, hyalin casts were graded 1 to 2, granular casts graded 2 to 3, erythrocytes graded 1 to 2, and pus cells varied from occasional cells to cells graded 2. *Blood:* Hemoglobin, 12 gm. per 100 cc.; erythrocytes, 3,900,000 and leukocytes, 10,000; urea, 40 mg. per 100 cc.; creatinin, 2.1 mg. per 100 cc.; CO₂ combining power was 51.3 vol. per cent; phenolsulphonephthalein excretion, 35 per cent. A serologic test of the blood for syphilis was negative. In the dilution test the lowest specific gravity was 1.006; in the concentration test the highest specific gravity was 1.022. An electrocardiogram showed left ventricular preponderance. A roentgenogram of the head indicated slight increase in intracranial pressure.

A small piece of pectoralis major muscle was removed for biopsy. The maximal changes were seen in the smallest arterioles (from 15 to 50 micra in diameter where the average ratio of wall to lumen was reduced to 1 to 1.1), there was moderate involvement of arterioles from 50 to 100 micra and less involvement of arterioles larger than 100 micra. In the smallest arterioles the medial nuclei appeared normal, but those of the intima were increased in number and tended to be polygonal. The arterioles were not tortuous. A diagnosis was made of subacute glomerulonephritis, arteriosclerosis, and cardiac hypertrophy. The edema disappeared during the period of rest in the hospital. At the time of dismissal the patient was advised to follow a salt-free diet of 40 gm. of protein, 2500 calories, with

fluids to the amount of 1000 cc. daily. Ferric citrate, grains 15, 3 times a day, was prescribed.

March 19, 1931, the patient returned to the clinic for observation. He had been feeling well and complained only of cramps in the calves of the legs at night at intervals during the 2 weeks previous to admission. Examination of the ocular fundi showed that the retinitis had improved considerably. The retinal arterioles were still moderately attenuated, but did not show definite sclerosis. The edema had subsided except for a few residual punctate exudates in the left macular region. One small hemorrhagic area was present in the left retina. The disks were slightly pale. The area of cardiac dullness extended 2 cm. to the right and 13 cm. to the left; the second aortic sound was not accentuated. Peripheral sclerosis of the rubbery type was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 120 to 170 and a diastolic range of 60 to 110 mm. mercury. The specific gravity of the urine was 1.018, albumin was graded 3, there was no sugar, hyalin casts were graded 1 and granular casts graded 2, erythrocytes graded 1 to 2 and pus was graded 1. *Blood:* Hemoglobin, 10.3 gm.; erythrocytes, 3,720,000, and leukocytes, 11,300; urica, 122 mg.; creatinin, 5.4 mg.; cholesterol, 303 mg., and serum proteins, 5.5 gm. per 100 cc., and the return of phenolsulphonephthalein was slight. In the dilution test the lowest specific gravity was 1.008, and in the concentration test the highest was only 1.014. A roentgenogram of the head was negative.

A piece of muscle removed for a second biopsy at this time showed an average ratio of wall to lumen of 1 to 1.2; this change was again chiefly in the small arteries. The nuclei of the intima were less prominent than before, but one arteriole contained a definitely organized thrombus. A diagnosis was made of chronic progressive glomerulonephritis with at least temporary subsidence of the active involvement of the arterioles, and secondary anemia. April 9, 1931, the patient reported that his ankles had become somewhat swollen. We learned that this patient died February 9, 1932.

The appearance of the retinitis at the first examination suggested the presence of primary nephritis (probably subacute glomerulonephritis) rather than primary hypertensive disease. The course of the retinitis, its rather rapid healing without the development of definite sclerosis of the arterioles, further supported this view. The degree of change in the ratio of wall to lumen noted in the arterioles of the pectoralis major muscle is greater than one would expect in an ordinary case of glomerulonephritis, and disproportionate to the changes observed in the arterioles of the fundus. We believe that such changes are evidence of the widespread organic disease of arterioles which can occur in certain cases of glomerulonephritis. From the clinical standpoint, a diagnosis of glomerulonephritis seemed most likely. This corresponded well with the ophthalmoscopic observations.

CASE 3.—A man, aged 33 years, was admitted to the clinic August 24, 1931, with a complaint of pain in the back of the neck, weakness and shortness of breath. In 1918 he had had a severe attack of influenza following which he did not feel as well as formerly. Seven years previous to admission he commenced to have frontal headaches which were characterized by a feeling of pressure inside the head and accompanied by vomiting that resembled the projectile type. The headaches usually lasted for about 6 hours, and occurred about 3 or 4 times a year until 2 years preceding admis-

sion, after which they occurred about once a week. Four months previous to admission he had had another attack of influenza followed by steady aching pain in the neck posteriorly which continued to trouble him. Albuminuria was found at the time of the onset of the headaches. For a year preceding admission, weakness, vertigo and dyspnea had developed after exertion. In the morning he also noticed puffiness beneath the eyes and in the fingers. He did not complain of disturbance of vision.

Central vision was approximately normal, but was not accurately tested as the patient was seen in bed at the hospital. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed residual angiospastic retinitis. The disks were full, somewhat blurred, and rather pale with some proliferation of connective tissue. A few punctate exudates of residual edema were present in the retina. The arterioles were narrowed and the retina around them appeared to be thickened. Sclerosis, graded 2, was present, but was mainly of secondary, postretinitic type. The lungs appeared to be normal. The heart was enlarged, graded 2; there was a faint apical systolic murmur, a basal systolic murmur, and the pulmonary sound was greater than the aortic second sound. Peripheral sclerosis was graded 1. The blood pressure studied over a period of 24 hours showed a systolic range of 140 to 200 and a diastolic range of 88 to 140 mm. mercury.

Laboratory Test. The specific gravity of the urine was 1.010, albumin was graded 4, there was no sugar, and erythrocytes were graded 2. Blood: Hemoglobin, 12.1 gm. per 100 cc.; erythrocytes, 3,760,000 and leukocytes, 6000; urea, 54 mg. The return of phenolsulphonephthalein was 45 per cent. A serologic test of the blood for syphilis gave negative results. The electrocardiogram showed left ventricular preponderance, diphasic *T* wave in Lead II and inverted *T* wave in Lead III.

A diagnosis was made of chronic glomerulonephritis with diffuse vascular disease, marked hypertension, and secondary anemia.

The fact that the retinitis in this case had probably been of short duration, and that it had healed without leaving characteristic arteriolosclerosis, suggested that it had been associated primarily with glomerulonephritis. The presence of a moderate grade of arteriolosclerosis, even though not typically hypertensive, would indicate, however, definite organic injury to the systemic arterioles which might warrant the diagnosis of primary hypertensive disease, or at least glomerulonephritis with secondary vascular injury. The long history of albuminuria with headaches and vomiting was more suggestive of glomerulonephritis. This was in accord with the findings in the fundi.

CASE 4.—A man, aged 35 years, was admitted to the clinic October 27, 1931. In April, 1929, he had strained his back when at work. Two weeks later he noticed hematuria, which continued for a period of 2 weeks. Two months later severe intermittent pain commenced in the right lumbar region and radiated anteriorly. Laparotomy was performed elsewhere a short time later. The abdomen was said to be full of blood, and the right kidney was low and was punctured. The blood was removed and no further treatment was given. The patient made a good recovery, except that he urinated once or twice at night. The systolic blood pressure at that time was 240. For a year previous to admission he had had occipital headaches in the morning, and some impairment of vision. The nocturia had increased. During the 2 weeks preceding admission he had noted hematuria again. There was nothing further of significance in the history except that at the age of 29 he had had scarlet fever.

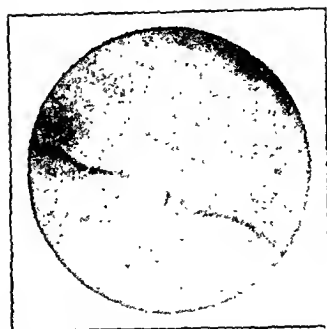


FIG. 1.—Case 4. Recent thrombosis of a small superior nasal arteriole.



FIG. 2.—Organized thrombus with complete obliteration of a small superior temporal arteriole.

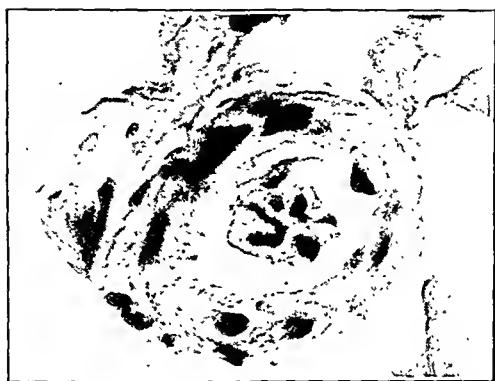


FIG. 3.—Case 4. An arteriole from the pectoralis major muscle removed at biopsy ($\times 675$); partial occlusion by organized thrombus may be seen.



FIG. 4.—Case 4. An arteriole from the pectoralis major muscle; an increase in number and size of nuclei of the intima and media and almost complete obliteration of the lumen may be noted.

Vision of the right eye was 6/20 and of the left, 6/7. The pupils, reflexes and peripheral fields of vision were normal. Ophthalmoscopic examination revealed angiospastic retinitis in the stage of commencing resolution. The disks were slightly pale. The peripapillary retinae was mildly edematous. Scattered cottonwool patches and hemorrhagic areas and incomplete macular stars were present in the retina of both eyes. The arterioles were moderately attenuated and irregular. The sclerosis, graded 2, was not typically hypertensive, but the presence of recent thrombosis, not yet organized, in one small arteriole in the left retina suggested the existence of active disease of the intima. The examination of the lungs gave negative results. The area of cardiac dullness extended 2 cm. to the right and 10 cm. to the left of the midsternal line; there was a systolic murmur at the apex and also a basal systolic murmur. The aortic second sound was accentuated, graded 2. Peripheral sclerosis was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 200 to 230 and a diastolic range of 95 to 135 mm. mercury.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 3, there was no sugar, erythrocytes were graded 4 to 5, and pus was graded 1. *Blood:* Hemoglobin, 11.7 gm. per 100 cc.; erythrocytes, 4,360,000; leukocytes, 6900; urea, 30 mg.; creatinin, 1.6 mg.; serum sulphates, 3.7 mg. The return of phenolsulphonephthalein was 30 per cent. The dilution test showed a minimum specific gravity of 1.008 and the concentration test a maximum of 1.016. A serologic test of the blood for syphilis gave negative results. An electrocardiogram revealed left ventricular preponderance and inversion of the *T* wave in Lead I and II.

Histologic study of the arterioles in a small piece of pectoralis major muscle removed for biopsy revealed definite and striking abnormalities. Numerous arterioles were seen in the sections, ranging from 25 to 200 micra in diameter. Marked thickening of the walls of the arterioles was noted in all those observed in the section, the average ratio of wall to lumen being 1 to 0.9. This ratio was quite constant, although a few arterioles had very little lumen. The arterioles were tortuous and there was a definite increase in the number and size of the nuclei of both intima and media. In one arteriole there was an organized thrombus almost entirely occluding the lumen and apparently compressing the wall. Cystoscopic examination disclosed right renal hematuria. There was marked deformity of the right pelvis with pyelectasis, the nature of which was indeterminate. The possibility of a postoperative polycystic kidney with pyelectasis and possibly ruptured cyst was not excluded.

A diagnosis was made of hypertension of Group 3, arteriolosclerosis, secondary anemia, myocardial degeneration and right renal hematuria. Whole blood was given intramuscularly daily for 3 days. Following this procedure the gross hematuria disappeared. On dismissal the patient was advised to follow a diet of 50 gm. protein, 2500 calories without extra salt, and fluids to the amount of 2000 cc. daily. Prescriptions were given for phenobarbital, grain $\frac{1}{2}$ 3 times a day, theobromin and sodium bicarbonate, grains 5 each 3 times a day, and for ferric citrate, grains 15 3 times a day.

We learned that this patient died February 7, 1932.

On the basis of the evidence of actual arteriolosclerosis, the retinitis was considered to be due to primary hypertensive disease. It seemed likely that this retinitis would not heal completely, but would gradually become the chronic obliterative arteriolosclerotic type. The appearance of the arterioles in the biopsy of muscle was typical of that seen in many cases of severe progressive hypertensive disease in the active phase, uniform, striking reduction in

the ratio of the wall to the lumen and definite increase in the number and size of nuclei of the intima and media. It is of interest to note that there was thrombosis of an arteriole in both retina and pectoralis major muscle. These thromboses may be due to prolonged vasospasm, but it seems more reasonable to suppose they are secondary to the definite organic arterial changes. The clinical impression also was that the primary condition could be attributed to diffuse arterial disease with hypertension. The hematuria was evidently distinctly local. It was not deemed advisable to investigate this any further because of the condition of the patient.

CASE 5.—A woman, aged 24 years, was admitted to the clinic October 13, 1930, complaining of headaches and amenorrhea. Headaches had commenced in October, 1928. They involved the vertex and sometimes the occipital region and occurred usually in the morning. A short time previous to admission the headaches had become more severe and of longer duration. One year previous to admission the systolic blood pressure was 150. During the 6 months previous to admission she had urinated 3 times nightly. Amenorrhea had been present for 2 years preceding admission to the clinic.

The skin was dry. Vision of the right eye was 6/10, and of the left eye, 6/7. The pupils, reflexes and fields of vision were normal. Ophthalmoscopic examination revealed acute retinitis similar to that seen in cases of subacute glomerulonephritis. Some of the retinal arterioles showed a suggestion of spasm, but definite generalized angiospasm was not demonstrable. Mild peripapillary edema, greater in the left eye, and a few cottonwool patches and hemorrhagic areas were present. Pus was expressed from the tonsils. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 11 cm. to the left; the second aortic sound was accentuated, graded 1. Slight peripheral sclerosis was present. The blood pressure studied over a period of 24 hours showed a systolic range of 150 to 190 and a diastolic range of 80 to 145 mm. mercury. Purpuric-like lesions of the skin were noted over the legs and feet.

Laboratory Tests. The specific gravity of the urine was 1.016, albumin was graded 2, there was no sugar, and there were a few erythrocytes observed on one occasion. *Blood:* Hemoglobin, 15.4 gm. per 100 cc.; erythrocytes, 4,480,000; leukocytes, 5700; urea, 26 mg. per 100 cc. of blood; the return of phenolsulphonaphthalein was 45 per cent. In the dilution test the minimum specific gravity was 1.001 and in the concentration test the maximum was 1.035. A serologic test of the blood for syphilis gave negative results. The basal metabolic rate was -13 and -4. The electrocardiogram showed left ventricular preponderance.

The arterioles in a piece of pectoralis major muscle removed for biopsy showed an average ratio of wall to lumen of 1 to 1.6. This change was slight but quite constant. The arterioles were moderately tortuous. The nuclei of the media and intima appeared large but were not increased in number. A diagnosis was made of severe essential hypertension, amenorrhea and infected tonsils. October 28, 1930, tonsillectomy was performed. At the time of dismissal the patient was advised to follow a diet of 50 gm. protein, 1500 calories without extra salt.

The patient returned to the clinic February 26, 1931, complaining that headaches had persisted. She was troubled somewhat with restlessness. The vision was 6/6 in each eye. The fundi showed the retinitis to be more definitely of the angiospastic type. The arterioles were generally constricted with some irregularity peripherally which was spastic rather than defin-

itely sclerotic. The disks were rather pale and mildly edematous with elevation of about 1 diopter. A few cottonwool patches and hemorrhagic areas were present in the retina. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 12 cm. to the left; the second aortic sound was accentuated, graded 2. Peripheral sclerosis was slight. The systolic blood pressure was 175 and diastolic 130 mm. mercury.

Laboratory Tests. The specific gravity of the urine was 1.017, albumin was graded 2, there was no sugar and there were a few erythrocytes and pus cells. *Blood:* Hemoglobin, 18.2 gm. per 100 cc. of blood; erythrocytes, 4,000,000; platelets, 130,000; coagulation time, 4 minutes, and bleeding time $2\frac{1}{2}$ minutes; urea, 24 mg. per 100 cc.; the return of phenolsulphone-phthalein was 40 per cent.

A diagnosis was made of essential hypertension of severe benign type with vasospastic features. On dismissal the patient was advised to follow a diet similar to that previously suggested, and in addition was given theocalcin 0.5 gm. 3 times a day.

The patient was again admitted to the clinic August 12, 1931. Her headaches were as troublesome as previously. For a month preceding admission she had noticed slight blurring of vision in the left eye, and she complained also of slight dyspnea. For 10 months previous to admission she had been too weak to continue her work. Examination at this time showed that vision was 6/6 in the right eye and 6/30 in the left eye. The retinitis had assumed the characteristics typical of malignant hypertension. The arterioles were definitely constricted and irregular. While some of the irregularity was still spastic, definite hypertensive sclerosis, graded 2, was present. The disks were hyperemic and edematous, elevated 1 diopter in the right eye and 2 diopters in the left eye. Cottonwool patches and hemorrhagic areas were present in the retina and an incomplete macular star had formed in the left eye. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 10 cm. to the left; the sounds were of good quality, there was a slight systolic impurity at the aortic area, the second aortic sound was accentuated, graded 2, and the second pulmonic sound was accentuated, graded 1. Peripheral sclerosis was graded 1 to 2. The blood pressure was 210 systolic and 145 diastolic.

Laboratory Tests. The specific gravity of the urine was 1.010, albumin was graded 2 and there was no sugar. *Blood:* Hemoglobin, 15.7 gm. per 100 cc.; erythrocytes, 4,000,000; leukocytes, 7500; urea, 24 mg., creatinin, 1.3 mg. and sulphates, 3.9 mg. per 100 cc. The return of phenolsulphone-phthalein was 45 per cent. The electrocardiogram showed left ventricular preponderance, diphasic *T* wave in Lead II and inverted *T* wave in Lead III.

A diagnosis was made of hypertension of Group 4 and arteriolosclerosis. Roentgen rays were applied over the thoracolumbar sympathetic chains. On dismissal the patient was instructed to follow treatment similar to that previously advised.

We learned that this patient died March 25, 1932.

At the first examination the retinitis was very recent, rather mild and showed only mild, rather localized angiospasm. It was impossible to distinguish the retinal picture from that seen in cases of acute or subacute glomerulonephritis. The relatively small amount of change in the arterioles of the pectoralis major muscle also suggests that at this time only slight organic changes had taken place in the general arteriolar bed. However, subsequent examinations revealed progression of the retinitis associated with the

development of generalized angiospasm and definite arteriolosclerosis, which placed it readily in the group associated with primary hypertensive disease. The possibility of primary glomerulonephritis was considered at the first admission to the clinic, as well as that of primary severe essential hypertension. Renal function was adequate, however, and there was no anemia. The presence of marked hypertension with so few other findings was atypical for glomerulonephritis. On the second admission the hypertension with its vasospastic features was predominant. It was not until the third visit, however, that the severe nature of the hypertension was appreciated.

CASE 6.—A man, aged 25 years, was admitted to the clinic February 2, 1932, complaining of attacks of severe pain in the epigastrium and in the right upper quadrant of the abdomen, of 3 years' duration, and of dizziness and weakness. The abdominal pain was intermittent, lasting half an hour to 2 days and was not related to meals. It usually troubled him for about 3 days, recurred every 3 months, and was accompanied by anorexia, nausea and vomiting. In December, 1931, he had had his severest attack of pain, with vomiting of old blood, syncope and tarry stools, and an icteric tint to the skin. The icterus persisted for a month. At the time of admission he complained of a slight amount of pain, and of weakness and dizziness. For 2 weeks preceding admission he had had severe frontal headaches. For 2 weeks in December, 1931, the vision of the right eye was impaired. It gradually improved, however, almost to normal. For 3 weeks preceding admission, there had been some impairment of vision of the left eye. Marked dyspnea on exertion had followed the last attack of pain. He had been on a diet consisting largely of milk and eggs, but obtained little relief from the symptoms. For the last 2 months he had urinated once or twice a night. Transient pains in the arms and legs had been present for 6 weeks preceding admission.

Vision of the right eye was 6/7 and of the left eye, 6/30. The pupils, reflexes, and peripheral fields of vision were normal. Ophthalmoscopic examination revealed active angiospastic retinitis in each eye, with some evidences of commencing resolution. The optic disks were relatively anemic and their nasal margins were mildly edematous with elevation of 1 diopter. Hemorrhagic areas, cottonwool patches, and a few punctate spots of residual edema were present in the retina of both eyes. Localized areas of edema and pigment proliferation were visible in the choroid. The arterioles of the retina were generally constricted and markedly irregular, with evidences of active sclerosis, graded 3. A recent thrombus was seen in a small inferior arteriole of the left eye. A small temporal arteriole of the right eye was occluded apparently by an organized thrombus. The tonsils were hypertrophied. Examination of the lungs gave negative results. The area of cardiac dullness extended 3 cm. to the right and 13 cm. to the left; there was a faint systolic murmur at the aortic area, and the second sound was accentuated, graded 2. Peripheral sclerosis was graded 2. The blood pressure studied over a period of 24 hours showed a systolic range of 190 to 220 and a diastolic range of 100 to 145. Tenderness was present in the left portion of the epigastrium and under the right costal margin.

Laboratory Tests. The specific gravity of the urine was 1.018, albumin was graded 3, and there was no sugar. *Blood:* Hemoglobin, 11.1 gm. per 100 cc.; erythrocytes, 4,140,000; leukocytes, 8600; urea, 38 mg., sulphates, 5.5 mg. per 100 cc. A serologic test of the blood for syphilis gave negative results. The response after a test meal was normal. An electrocardiogram showed left ventricular preponderance and inversion of the *T* wave in all derivations. A roentgenogram of the thorax was negative except for slight

cardiac enlargement. Roentgenograms of the gall bladder and stomach were negative. A diagnosis was made of malignant hypertension and secondary anemia.

During the period of observation in hospital the patient had an attack of epigastric pain radiating substernally, associated with slight dyspnea. Two weeks after the first examination, the general appearance of the retinitis was the same, but the thrombus in the small arteriole in the left eye was undergoing organization and collateral circulation was being formed through the dilatation of a number of fine capillaries. The presence of an active lesion of the intima in the arterioles of the retina in this case favored the diagnosis of primary hypertensive disease. It was impossible to say at this stage whether the disease would develop into progressive hypertension (Group 4), or whether compensation might occur. The possibility of compensation with the development of relatively inactive arteriolosclerosis was suggested by the rapid development of collateral capillary circulation. The etiology of the abdominal pain was undetermined. It is possible that it was due to the vascular disease. It is of interest that the history which could be attributed directly to the hypertension was extremely short.

Comment. All these patients were rather young (24 to 38 years). Five had a fairly short history. Four of the 6 patients gave headache as a prominent symptom. Visual impairment was also noted by the same number. Four had mild secondary anemia which was of questionable significance. The electrocardiogram showed evidence of serious involvement in 2 cases. In 2 of the 6 cases glomerulonephritis apparently was primary, and the condition in the remainder could best be classified as primary diffuse arterial disease with hypertension. Two patients gave a history of gross hematuria. In Case 2 it seemed definitely related to the renal disease. In Case 4 apparently the local renal involvement was undetermined, and was distinct from the hypertension. One patient (Case 2) gave a definite history of edema, undoubtedly related to the nephritis. Two patients gave a history of puffiness of the eyes which was of questionable significance. Four of the patients died within 17 months of the discovery of the angiospastic retinitis.

The part played by angiospasm in the causation of retinitis in cases of toxemia of pregnancy has been demonstrated by Haselhorst and Mylius, and confirmed by one of us (Wagener). Continuance of the angiospasm in these cases for a relatively short period can be shown to result in definite organic injury to the walls of the arterioles in the retina. There is strong evidence in a considerable number of cases that there is similar organic injury to the systemic arterioles throughout the body. The occurrence of a similar chain of events in hypertensive disease is strongly suggested by the appearance and course of the changes in the retina in the case reported by Koenigsberger and Bannick and in the group of cases

here described. The significance of angiospasm in the development and course of primary hypertensive disease and of glomerulonephritis is emphasized by the rapid progression of the disease in these cases.

Conclusions. 1. Acute diffuse angiospastic retinitis can occur in both glomerulonephritis and primary hypertensive disease.

2. The course of the retinitis and its associated arteriolar lesions will often indicate the degree of organic injury to the systemic arterioles.

3. The retinitis is of serious prognostic significance.

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STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA.

A REPORT OF THREE CASES WITH REMARKS UPON THE CLINICAL ASPECTS.

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COARCTATION of the aorta is a rather rare congenital anomaly in which there is a complete or partial occlusion of the lumen of the aorta, and which in the adult type, described here, occurs at or near the insertion of the ductus arteriosus Botalli into the aorta.

The pathologic anatomy and clinical features of coarctation of the aorta have been admirably presented by Abbott¹ in her classical work published in 1928, and by others.² Its pathologic physiology has been studied in the greatest detail by Blumgart and his associates.³ The typical roentgenographic findings have been described by Rösler,² Railsback and Dock,⁴ Fray⁵ and Ernstene and Robins.⁶

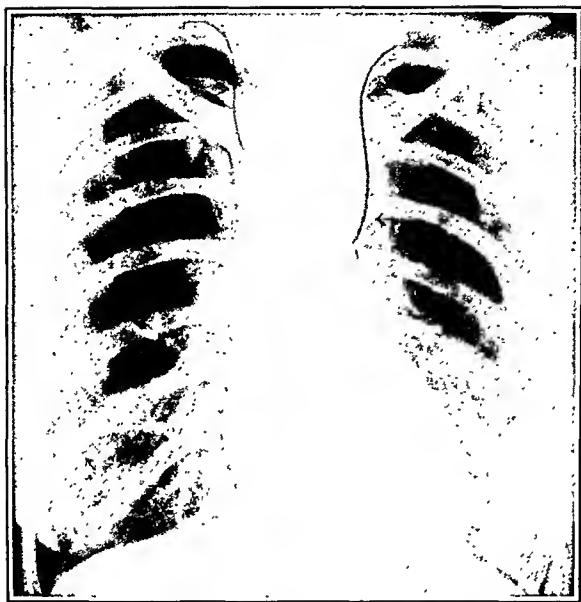


FIG. 1.—A stereoroentgenogram of the chest (M. A. E.).
(Slightly retouched.)

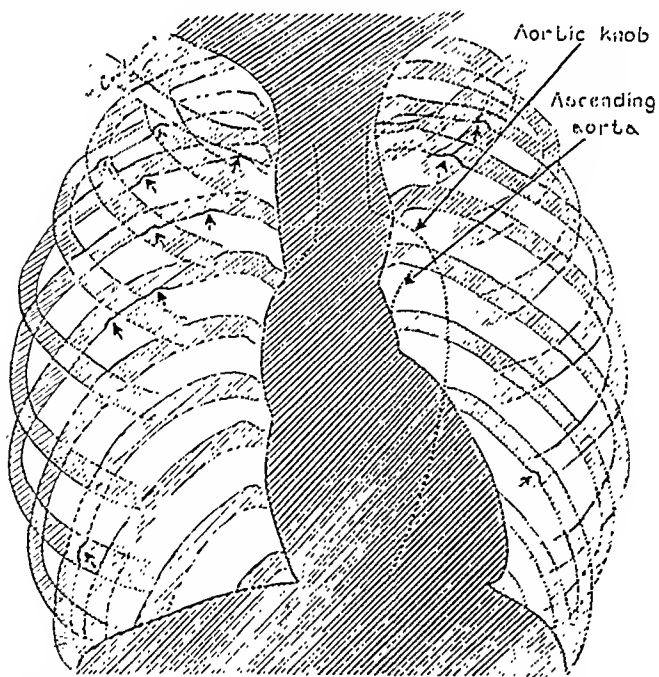


FIG. 2.—A diagrammatic sketch of Fig. 1, showing the roentgenologic signs of coarctation and in dotted lines, the aortic shadow in hypertensive heart disease.

Three typical cases have been observed at this hospital during the past $1\frac{1}{2}$ years, during which time there have been 2845 admissions to the medical service. In each instance the signs were overlooked by more than one observer, and in 2 of the cases the diagnosis was first made by Roentgen ray. These cases are reported to re-emphasize the clinical features which should enable one to make the diagnosis at the bedside and to comment on some interesting corollaries.

Case Reports. CASE 1.—H. B. M. (Med. No. 41118), aged 33 years, white, American intern, entered the hospital on May 20, 1932, for study. His life thus far had been entirely normal. In 1917, at the age of 18 years, he applied to a railroad company for employment but was not accepted because of a systolic murmur. Subsequently he volunteered for service in both the army and navy and was refused for the same reason. During the years 1917 to 1923 he led an extremely active physical life, spending the summers on a farm where he was able to carry on the most strenuous tasks without embarrassment.

In 1923 he entered college, where the routine physical examination again disclosed a systolic murmur, and for this reason he was not permitted to take part in vigorous athletics.

During 1927, his first year in medical school, he made 17 out of a possible 18 points in a Snyder circulation test. Throughout his medical school career he followed the custom of the medical students in devoting $\frac{1}{2}$ hour in the afternoon to recreation in the form of squash, without any difficulty.

The systolic murmur and a moderately elevated blood pressure were consistently found at the routine physical examinations, but the diagnosis of coarctation of the aorta was not definitely established until November, 1930, when a roentgenogram was taken to ascertain if he had any unusual cardiac enlargement.

Physical examination revealed moderate suffusion of the facies, disproportionately greater development of the musculature of the trunk and upper extremities than that of the lower. The thorax was not unusual to inspection except for a vigorous suprasternal pulsation, more marked toward the right. There were no abnormal pulsations visible over the chest anteriorly or posteriorly. On palpation, however, definite arterial pulsations could be made out posteriorly on both sides over an area extending from the 2d to the 9th interspaces and from the spinous processes to the mid-axillary line. In the interseapular area on both sides of the spinal column a harsh, blowing systolic murmur could be heard. It was loudest in the left interseapular area opposite the spine of the scapula. No pulsations could be felt over the chest anteriorly. The heart was not abnormal to percussion. The apex impulse could not be seen or felt. The supracardiac dullness measured 5 cm. in the 2d interspace. There was a harsh, rough, blowing precordial systolic murmur, best heard just over the xiphoid process. The radial pulses were equal, regular and synchronous at a rate of 66 per minute. The vessel walls were not thickened, beaded or tortuous. A definite pulsation could be felt in the popliteal and dorsalis pedis arteries. The pulsation of the abdominal aorta could not be felt while that of the femoral arteries was very feeble on the left side and barely perceptible on the right. The femoral pulse was detectably delayed in comparison with the radial pulse. Blood pressures in the recumbent posture were: right arm, 150/80; left arm, 154/90; right leg (popliteal), 122/94; left leg (popliteal), 120/90. By examination the lungs were entirely normal. The abdomen was not remarkable. There was no clubbing of the fingers. There

was a marked capillary pulsation in the fingers. No note was made of its presence or absence in the toes. No other congenital defects were found.

A roentgenographic examination on November 18, 1930, reported: A 7-foot film of the heart showed it was just inside the normal limits; the left ventricle was somewhat prominent and fluoroscopy showed a rather vigorous ventricular impulse. There was no other abnormality in contour, except that the descending aorta was not visible. The ribs showed marked indentation of the inferior borders quite similar to that seen in coarctation of the aorta. Measurements were Mr. 4.2, Ml. 10, G.V. 4.7, int. dia. 29.4 cm. A second examination on November 25, 1930, stated: Oblique views, both right and left, fail to show the aortic arch definitely. A.P. stereo on the Bucky diaphragm showed a definite flattening and a dimple in the 1st portion of the descending aorta just below the arch. There was widening of the supraortic shadow suggesting an increase in the size of the vessels. The vertebrae were apparently intact; the ribs showed the notching previously noted. Impression: Coarctation of the aorta. Electrocardiograms showed normal tracings.

The Wassermann and Hinton blood serum reactions were negative. Red and white blood cell counts were normal as was the urine examination. Skin temperature determined by the Tycos dermatherm showed the feet to be 0.7° cooler than the hands, whereas a similar simultaneous set of observations on a patient with a presumably normal circulation showed the feet to be 0.9° cooler than the hands.

CASE 2.—M. A. E. (Med. No. 40260), aged 32 years, female, single, white, American, unemployed factory worker, entered the hospital for the first time on January 8, 1932, with the complaint of abdominal pain of 3 years' duration. Her family history and past history were irrelevant. She had been perfectly well until 3 years ago, when she first noted knifelike, griping pain in the left lower abdominal quadrant, present almost constantly ever since, aggravated by food, partially relieved at times by soda and defecation. It was occasionally accompanied by sour eructations and vomiting. Two years ago her persistent abdominal distress and menstrual disorders led to an appendectomy and subsequently a bilateral salpingectomy. It was at this time that she first noticed slight dyspnea on exertion and weakness of the legs on moderate activity. This weakness has steadily increased until at the present time she is unable to walk $\frac{1}{2}$ block without experiencing a sensation of "knotty cramps" in the calves and a feeling that "her legs were going to double up beneath her."

Three months ago the abdominal symptoms again took her into another hospital where Roentgen ray examinations of the chest and gastrointestinal tract were reported as negative. The diagnosis at discharge was "neurasthenia, gastric." In January of this year she was referred to this hospital for study.

Physical examination revealed the following positive findings: the skin of the face and neck showed considerable vasomotor instability. The eyes were slightly prominent. The retinal arteries were normal. The thyroid was not palpable. There was a supernumerary nipple of the left breast but no other congenital anomalies. There was a forceful pulsation in the suprasternal notch. Carotid pulsations were accentuated on both sides of the neck. A blowing systolic bruit was heard in the supraclavicular area on the right. Pulsations could be seen in the interscapular area and felt from the 3d to the 9th intercostal spaces posteriorly on both sides. These pulsations were more marked on the left except in the region of the bellies of the latissimus dorsi muscles. In the interscapular areas a rough, blowing systolic murmur could be heard, the point of maximum intensity being over a small area, measuring 3 by 4 cm., just to the left of the 2d dorsal spine. By percussion the heart borders seemed slightly outside the

normal limits in size. Supracardiac dullness measured 6 cm. in the 2d interspace. At the apex auscultation revealed a soft, rumbling murmur early in systole which assumed a blowing character in late systole. This murmur was heard all over the precordium but best in the 3d left interspace. It was of less intensity than the murmur heard posteriorly. The radial pulses were equal, regular and synchronous; radial and brachial arteries were moderately thickened but not beaded or tortuous. The pulsations of the abdominal aorta could not be felt. Both femoral pulses were definitely palpable. The popliteal pulsations were not felt, but there were slight though definite pulsations over the dorsalis pedis arteries. Blood pressures in the recumbent posture were: right arm, 116/88; left arm, 135/90; right leg (popliteal), 102/88; left leg (popliteal), 100/88.

Stereoroentgenograms of the chest showed the lungs to be clear, except for a thickened septum around an azygos lobe at the right apex. The heart size was at the upper limits of normal, and showed a rather prominent first portion of the aorta which pulsated markedly under the fluoroscope. The aortic knob was less distinct than would be expected and there was an apparent depression in the border of the aortic shadow just below the knob. The vessels extending into the neck from the aorta were considerably enlarged. The ribs showed marked notching of the inferior borders with the smooth dense concavities characteristic of coarctation of the aorta.

A barium enema showed a normal colon. A gastrointestinal series was negative. Gastric analysis showed a normal free and total acid. Electrocardiograms showed left ventricular preponderance. The basal metabolic rate was +10. Urine, stool and blood examinations were not remarkable. The Wassermann and Hinton blood serum reactions were negative. Skin temperatures determined with the Tycos dermatherm showed the temperature of the feet to be 4° below that of the hands.

During the last week of her hospitalization and for the first 2½ months following discharge amidopyrin was found to be efficacious in relieving the abdominal distress, but she continued to have discomfort in her legs when ambulatory for ½ hour or more. During this period of time her brachial blood pressure was found to have risen to 152/120 in the left arm and 140/90 in the right arm. Pressures taken in the popliteal spaces remained essentially the same as those previously noted. When last seen, 4 months after discharge, she again complained of the previous abdominal pain, unrelieved by amidopyrin.

CASE 3.—J. C. (Med. No. 40134), an Italian housewife, aged 28 years, entered the hospital on December 18, 1931, complaining of recurrent attacks of palpitation, dyspnea and pain of 7 years' duration. The family history was entirely irrelevant.

She was born in Italy and insofar as can be ascertained her childhood and youth were uneventful. There was nothing abnormal about the catamenia. *Eight years ago* (at 20 years) she had 2 severe attacks of epistaxis which required the attention of a physician. *Seven years ago* she was awakened quite suddenly out of a sound sleep by a pounding in her neck and knifelike, constricting precordial pain, accompanied by marked dyspnea and finally relieved by a hypodermic injection. For a week afterward she suffered from headache and intermittent attacks of constricting, knifelike precordial pain. Since then attacks of this nature have occurred at intervals of about 3 months and have been almost invariably initiated by profound emotional upsets. They were followed by several days of temporal headache, dizziness, scotomata scintillans and occasionally syncope. Five years ago, with the first of her 5 pregnancies, she had what she described as a "dream shock" when she was suddenly awakened out of a sound sleep by the symptoms enumerated above. This "dream shock" differed from her usual attacks in that she noted the following morning that

her right eye deviated outward and her face seemed to be drawn to the left. A similar episode occurred a year later with her second pregnancy. Both pregnancies terminated in miscarriage. In each of these instances 3 months passed before her eye "straightened" and her face assumed its normal contour. Three subsequent pregnancies were full-term deliveries and not accompanied by "dream shocks." During the past 7 months nocturia, orthopnea and edema of the ankles have appeared. Throughout this period there have been intermittent attacks of sharp pain in the flanks radiating to both lower quadrants, lasting only a few moments, disappearing spontaneously.

She was first seen in the out-door department of this hospital in October, 1931, where a physical examination revealed evidence of cardiac insufficiency and she was thought to have essential vascular hypertension and mitral stenosis. A roentgenogram of the chest, taken on November 30, 1931, revealed the typical signs of coarctation of the aorta and she was sent into the hospital for further study.

On *physical examination* her general appearance was not remarkable, except for moderately suffused facies and a warm skin, which was slightly flushed and moist. The pupils were equal and regular, and reacted promptly to light and on accommodation. The extraocular movements were normal. Ophthalmoscopic examination showed marked caliber changes of the retinal arteries, with moderate nicking at the arteriovenous crossings, but no exudate or hemorrhage. There was no evidence of facial palsy. The tongue protruded in the midline. The thyroid was not palpable. A loud systolic murmur was heard above the suprasternal notch, extending up into the vessels of the neck on each side to about the level of the hyoid bone, and in this region there was a marked arterial pulsation. The thorax appeared normal to inspection except for definite visible pulsations in the interscapular region synchronous with the systole of the heart. On careful palpation pulsations were felt in almost all the intercostal spaces posteriorly. Over all these vessels a loud, harsh, systolic murmur was heard, loudest in the interscapular area. The lungs were negative. The heart was enlarged both to the right and to the left. The action was regular and the sounds were of good quality. Over the precordium there was heard a harsh, systolic murmur which was transmitted to the vessels of the neck. The first sound was markedly reduplicated and the aortic second sound accentuated and snapping. At the base there was also a faint but definite systolic thrill. The radial pulses were equal, regular and synchronous. The vessel walls were slightly thickened but not tortuous or beaded. Femoral pulsations were felt with difficulty on the right side only. The popliteal, posterior tibial and dorsalis pedis arterial pulsations could not be felt in either leg. Pulsation of the abdominal aorta was not felt. Blood pressure determinations were: right arm, 300/125; left arm, 290/130; right leg, 135/100; left leg, 110/90. The blood pressures in the legs were taken in the femoral triangles, as they could not be obtained in the popliteal spaces. There was no clubbing of the fingers. There were no pathologic reflexes. There was slight pitting edema over the tibiae.

A stereoroentgenogram of the chest showed definite cardiac enlargement to the right and left, with an apparent pleuropericardial adhesion on the right. The arch of the aorta was indistinct and there was a soft tissue shadow with the shadow extending upward on the left of the spine in the aortic area. The descending aorta was not visible. Several of the ribs showed small, smooth concavities on the inferior borders. A 7-foot heart plate showed it to be slightly above normal limits in size, with a rounded, blunt left ventricle. The previous findings of supraortic shadow on both sides and of erosions of the inferior margins of the ribs were confirmed. The heart measurements were Mr. 5.2, Ml. 8.2, G.V. 5, int. dia. 25.4 cm.

An A.P. stereo of the chest showed a definite notch in the lateral edge of the descending aorta just below the arch opposite the 5th thoracic vertebra. The basal metabolic rate on admission was +46, which in the course of 10 days of hospitalization came down to +8 without specific medication. Electrocardiographic tracings showed left ventricular preponderance. Clinical pathology was not remarkable. The Wassermann and Hinton blood serum reactions were negative. A urinary phthalein test showed 60 per cent excretion of the dye in 2 hours and 10 minutes by the intramuscular method.

Skin temperatures as determined by the Tycos dermaterm showed that the patient's hands and feet were essentially the same temperature, the latter being 0.4° warmer than the former, whereas in a normal control the feet were 1.2° warmer than the hands (in each instance the dorsi of the hands and of the feet were compared).

Since discharge from the hospital the patient has been seen at monthly intervals in the out-door department, and has continued to suffer from the same symptoms as on admission, but to less marked degree.

Comment. In considering these 3 cases from the point of view of diagnosis, we find that they have certain points in common with those reported by other observers, particularly in recent years.

First in the history one discovers that there were no symptoms referable to the cardiovascular system throughout childhood and youth. One of them, H.B.M., had never suffered any circulatory embarrassment. The second, M.A.E., had symptoms only since the age of 30 years, notably intermittent claudication, slight dyspnea and abdominal pain of a vague character. The third, J.C., developed symptoms of hypertensive cardiopathy at the age of 21 years.

The salient point to be drawn from these cases is the fact that evidence of hypertension or hypertensive disease in a young adult without renal disease should suggest the possibility of coarctation of the aorta before considering the case as one of idiopathic hypertension.

A less important, though none the less striking, feature is intermittent claudication of the legs in the same period of life. These symptoms in the second case were undoubtedly due to an inadequate circulation to the lower extremities and the coincident occurrence of abdominal symptoms may permit the inference that the cause of them could be on a similar basis. Her repeated abdominal operations without relief lend weight to this impression.

While the history may suggest coarctation of the aorta, there are certain physical characteristics of these cases that are pathognomonic of the condition. The presence of these should enable one to make the diagnosis. These signs are:

1. A harsh, blowing systolic murmur heard in the interseapular area just to the left of the spine and less intensely over the preeordium.
2. Palpable and occasionally visible arterial pulsations over the posterior aspect of the thorax.

3. The blood pressure in the brachial artery is higher than that of the femoral (a reversal of the normal condition).

4. Normal or bounding arterial pulsations in the upper extremities with absent or feeble pulsations in the lower extremities.

5. Absence of a palpable pulsation in the abdominal aorta in the presence of a forceful systolic thrust in the suprasternal notch and vessels of the neck.

Equally striking are the roentgenographic findings, illustrated by Figs. 1 and 2:

1. Bilateral scalloping of the inferior borders of the ribs.

2. A blunt left ventricular shadow without the prominent aortic knob usually associated with hypertension.

3. A widened supraortic shadow.

4. Depression or dimpling of the left border of the descending aorta just below the point where the aortic knob is normally seen.

Laboratory studies and electrographic tracings do not contribute to the diagnosis. As would be anticipated, there is no remarkable contrast between the skin temperatures of the upper and lower extremities.

It is interesting to note that 2 of our cases were thought to have hyperthyroidism because of the presence of flushed facies, warm, moist skin, emotional instability, hyperactive heart, precordial systolic murmurs with a pulsation and bruit in the region of the thyroid gland.

With the diagnosis established, one can make predictions with reasonable accuracy in regard to the prognosis and probable cause of death.

The prognosis should be guided by symptoms and signs referable to circulatory failure and symptoms of hypertensive disease. These criteria are illustrated by our cases. H.M., who is asymptomatic, has a normal heart size by physical examination and Roentgen ray, and no left ventricular preponderance by electrocardiograph, has an apparently adequate collateral circulation as judged by the absence of symptoms, and only a moderate brachial hypertension. His outlook is certainly the best. M.E., who has slight dyspnea, intermittent claudication and an enlarged heart by physical examination (though a 7-foot film showed no enlargement), left ventricular preponderance by electrocardiograph, less easily palpable vessels in the legs, a degree of brachial hypertension similar to that of H.M., has probably a less favorable prognosis. J.C., on the contrary, with her marked symptoms of hypertensive cardiopathy, cardiac enlargement by physical examination and Roentgen ray, marked brachial hypertension and imperceptible pulses in the lower extremities certainly has a gloomy prognosis.

The probable mode of death as given by Abbott¹ in a series of 200 autopsied cases in the order of frequency is: (1) Cardiac failure; (2) rupture of the aorta; (3) cerebral accidents; (4) subacute bac-

terial endocarditis. Of her cases 74 per cent died before the age of 40 years, with an almost equal distribution (total 69 per cent) in the 2d and 4th decades.

Summary. Three typical cases of coarctation of the aorta are presented and discussed briefly with emphasis on the history and physical findings.

ADDENDUM.—During the first week in November, 1932, two more cases of Coarctation of the Aorta have been called to our attention. These cases were diagnosed in the Out-Door Department on purely clinical grounds without recourse to roentgenograms except for confirmation.

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A SIMPLE TEST FOR CAPILLARY RESISTANCE: THE "FLICKING" TEST.*

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ALTHOUGH petechiæ and vibices were observed by Hippocrates, it was not until 1556 that their presence was dissociated from pestilential fevers by Amatus Lusitanus,¹ who called the condition "morbus pulicaris absque febre" (flea-like disease without fever). At times great difficulty was experienced in differentiating between an individual with purpuric manifestations and one infested with fleas. Following flea bites, petechiæ and at times ecchymoses and hematomas developed. In 1657 La Rivière,² to whom we owe the first complete description of purpura, mentioned petechiæ. Sir John Pringle,³ in the 18th century, noted their presence in the arms

* Read before the Cosmopolitan Club, Philadelphia meeting, on February 6, 1932. Prepared under a grant from the J. Ewing Mears Research Fund.

of patients with jail or hospital fever after a tourniquet had been applied for venesection.

The first test for capillary resistance was devised by Koch⁴ in 1890. This consisted of multiple intradermal punctures with a needle, after which, in certain cases, petechiæ appeared. It is significant that Koch described his test as of special value in purpura. A few years later Hecht⁵ devised a simple instrument to test the resistance of the skin capillaries by the application of negative pressure. It consisted of a 3-way tube with a stopcock in the position leading to a small metal syringe; to the other tubes a glass cup and a mercury column were connected. With this method Hecht could create a negative pressure in the cup when applied against the skin and read the amount of pressure on the mercury column. In 1929 Silva-Mello⁶ designed a more elaborate instrument which he called the "capillarresistometer" based on Hecht's invention. Schultz⁷ discovered that striking the skin of the tibia or sternum resulted in the appearance of petechiæ. In 1911 Weill⁸ brought out the tourniquet test ("signe du lacet") and demonstrated the appearance of petechiæ below the tourniquet. In the same year Rumpel and Leede⁹ (German), Rocco and Frugoni¹⁰ (Italian) and in 1914 Hess¹¹ (American) described similar tests. Rumpel and Leede studied this test in connection with scarlet fever and Hess with scurvy. Frugoni and Weill described the test as associated with purpura. Longo¹² claims that Hess, in 1913, demonstrated the appearance of hematomata in purpuric patients after subcutaneous injections of physiologic salt solution, but no record of such a test was found in the literature.

In our studies we have found the capillary resistance test to be positive in a large percentage of supposedly normal individuals. We have noted that certain factors, such as time of the year, diet, infection and constitution, affect the incidence of positive results. These data will appear in another article. The flicking test was suggested by one of us (H. W. J.) because while percussing the heart directly in 1 of our patients with purpura the organ was outlined by petechiæ. The test is performed as follows:

The tourniquet is applied 2 to 3 inches above the elbow for 5 minutes as for the capillary resistance test. After 4 minutes, by flicking the middle finger (Fig. 1) against the distended vein 3 or 4 times petechiæ appear. A control may be performed above the tourniquet by flicking with similar force, with a resultant erythema, but in most instances no petechiæ appear (Fig. 2).

At the suggestion of Dr. Krumbhaar,¹³ the flicking was performed over an area between the veins. The result was positive, although not as marked as when the vein was flicked (Fig. 2b).

In cases with active purpura it may not be necessary to apply a tourniquet. Flicking may produce petechiæ in almost any part of the body.

The flicking test was performed in 108 normal individuals on whom the capillary resistance test was performed. A comparison brought out the following points: Of the 108 individuals, 55 had

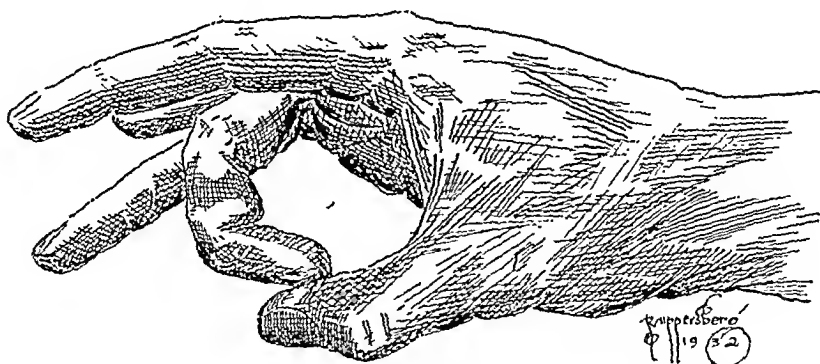


FIG. 1.—Position of the fingers for the performance of the test.

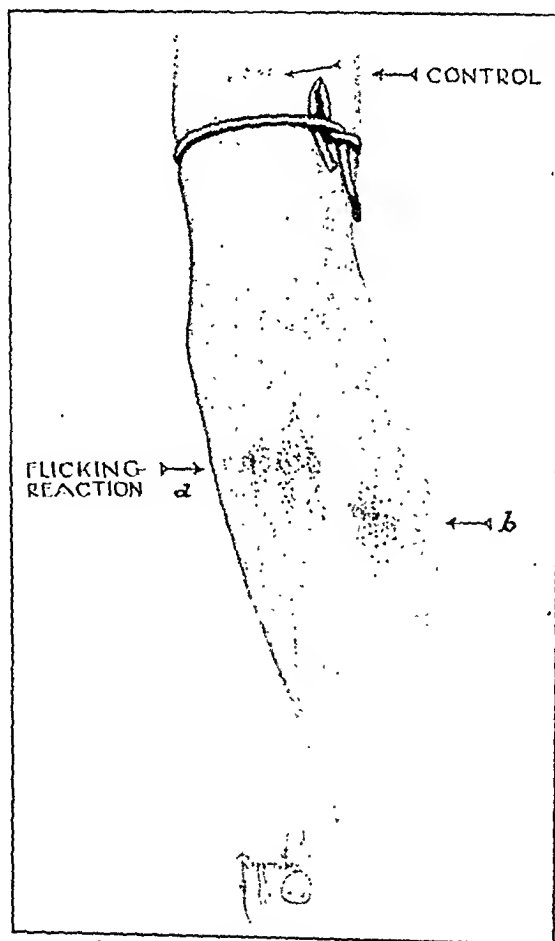


FIG. 2.—Appearance of the arm after performance of the "flicking" test: *a*, over a vein; *b*, in area without large veins.

both negative capillary resistance and flicking tests; 33 had a negative capillary resistance test and also a positive flicking test. In each instance of a positive capillary resistance test there was also a positive flicking test. On the other hand, not all cases in which the flicking test was positive showed a positive capillary resistance test. The total in this group having positive flicking tests was 53 (49 per cent) of the normal group.

It is of interest to note that there was an equal frequency of positive flicking tests in those that gave a personal or family history of hemorrhagic disposition, as well as those whose family or personal history was negative. Of 30 individuals who gave a history of frequent nosebleed, 18 showed a positive flicking test, whereas only 13 had a positive capillary resistance test. Of 7 who stated that they bruised easily, 4 gave a positive flicking test, while only 2 had a positive capillary resistance test.

The flicking test often is positive when the capillary resistance test is negative. It is 100 per cent positive in those cases in which the capillary resistance test (tourniquet test) is positive. It is, therefore, more sensitive than the capillary resistance test. In every case of acute purpura that has come under our observation the flicking test has been positive. During the convalescent period we utilize the capillary resistance as an indication of the condition of the capillaries. At times hemorrhagic phenomena are present even though the tourniquet test is negative. The flicking test in these cases remained strongly positive.

Summary. 1. The first mention of petechiæ in relation to a condition resembling purpura hemorrhagica was made by Amatus Lusitanus in 1556.

2. The first test for capillary resistance was devised by Koch, in 1890, and consisted of intradermal punctures with a needle.

3. In 1911 Weill brought out the tourniquet test. In the same year Rumpel and Leede, Rocco and Frugoni, and Hess, in 1914, described similar tests.

4. A new test, the flicking test, is described. The advantages are that it is easy to perform, yields more positives than the capillary resistance test (tourniquet test) and is positive after the capillary resistance test is negative.

5. In every patient with acute purpura hemorrhagica the flicking test was positive. In some of these cases the tourniquet test was negative.

6. In the study of a series of normal individuals the flicking test was found to be positive more often than the tourniquet test.

7. The positive flicking test indicates that the capillaries or venules rupture or become more permeable, resulting in the appearance of petechiæ. About 49 per cent of supposedly normal individuals show this phenomenon in the spring of the year.

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STUDIES OF ANEMIA IN PREGNANCY.

III. THE ETIOLOGIC RELATIONSHIP OF GASTRIC SECRETORY DEFECTS AND DIETARY DEFICIENCY TO THE HYPOCHROMIC AND MACROCYTIC (PERNICIOUS) ANEMIAS OF PREGNANCY AND THE TREATMENT OF THESE CONDITIONS.*†

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THE occurrence of moderate grades of anemia during pregnancy has long been considered physiologically normal. In the preceding papers of this series,^{1,2} evidence obtained from the study of a group of normal pregnant women was presented which indicated

* A preliminary report of these studies was presented before the American Society for Clinical Investigation at Atlantic City, N. J., May 2, 1932.

† The expenses of this investigation were defrayed in part by the E. K. Lilly gift to the Harvard Medical School.

that true reduction in the *total* amount of hemoglobin in the maternal body (excluding the transient effect of hydremia) is found only in association with dietary deficiency or altered gastrointestinal function. Normal women in whom neither of these factors was present did not, in our observations, become anemic in pregnancy.

That severe and even fatal anemias may occur in pregnancy from no obvious cause has been known for a long time. In 1842 Channing,³ of Boston, reported a series of such cases and, although a number of these were probably primarily cases of puerperal sepsis, others were undoubtedly cases of uncomplicated anemia of pregnancy. Bibliographic reference to the voluminous literature on this subject has already been made.² It is obvious that pregnancy may occur during the course of anemia due to any number of known causes, and it is likewise true that hemorrhage or infection complicating pregnancy, parturition or the puerperium may produce as severe an anemia as may similar events in nonpregnant individuals. In particular, puerperal sepsis due to hemolytic streptococci or other organisms may be accompanied by rapidly progressive anemia associated with blood destruction. It has, however, been shown² that pregnancy need not aggravate the degree of preëxisting anemia. It has also been shown that *under controlled conditions* spontaneous recovery following parturition apparently does not occur in the anemias of pregnancy.

In this communication will be presented observations concerned with etiologic and therapeutic factors made upon 36 consecutive cases of severe anemia of pregnancy with less than 45 per cent (7 gm. per 100 cc.) hemoglobin, or less than 2,500,000 erythrocytes per c.mm., due to none of the usual obvious causes of anemia. These observations, made upon cases of marked anemia, confirm the conclusions previously drawn from the study of normal pregnant women and suggest that these anemias are due either to a lack of specific substances of the diet necessary for blood formation or to an abnormality of the gastrointestinal tract preventing the proper utilization of such specific substances or to a combination of these two factors, in the presence of an increased demand to supply the fetal blood requirements. The condition of 3 of these patients has previously been described in detail.⁴ The clinical histories and physical examinations of the 33 new cases so closely approximate those already given that they are not recorded here. The chief presenting symptoms were pallor, appearing usually about mid-pregnancy or later, a lack of sense of wellbeing and excessive fatigability. In the more severe cases edema, dyspnea and prostration were observed. Splenomegaly, disappearing with adequate treatment of the anemia, was observed 4 times and fever without demonstrable infection, similarly abating, was observed 6 times. The latter occurred only in the patients with macrocytic anemia. The seriousness of these anemias of pregnancy was manifested by the

TABLE 1.—ETIOLOGIC FACTORS AND RESPONSES TO THERAPY OF 36 PATIENTS WITH SEVERE ANEMIA OF PREGNANCY.

Case No.	Age (years.)	No. of births.	Type anemia.	State of gastric juice.	Diet.	Initial blood level.			After iron therapy.			Control period.		Response during control period.
						Hgb. per cent.	R. B. C. (mils.)	Hgb. per cent.	R. B. C. (mils.)	Duration of therapy (days).	Type.	Duration (days).		
1	34	13	Hypochromic	Achlorhydria	Good	33	2.87	81	4.60	38	*
2	25	2	Hypochromic	Achlorhydria	Poor	33	2.45	65	4.38	25	*
3	24	2	Hypochromic	Achlorhydria	Good	35	3.53	78	4.81	42	†
4	26	3	Hypochromic	Achlorhydria	Poor	42	4.83	87	7.34	95	No therapy	62	..	None
5	30	2	Hypochromic	Achlorhydria	Good	28	2.59	90	5.69	56	No therapy	10	..	None
6	39	6	Hypochromic	Achlorhydria	Good	31	2.16	98	6.61	70	No therapy	20	..	None
7	28	3	Hypochromic	Achlorhydria	Poor	36	3.33	91	5.16	47	No therapy	10	..	None
8	34	1	Hypochromic	Achlorhydria	Good	37	3.64	†
9	22	4	Hypochromic	Achlorhydria	Good	41	3.30	85	3.92	45	†
10	33	8	Hypochromic	Achlorhydria	Good	43	3.33	70	5.09	52	No therapy	180	..	None
11	37	3	Hypochromic	Achlorhydria	Good	34	3.19	70	5.09	52	No therapy	180	..	None
12	32	7	Hypochromic	Achlorhydria	Poor	27	2.36	No therapy	150	..	None
13	32	7	Hypochromic	Achlorhydria	Poor	29	3.44	75	4.60	180	No therapy	60	..	None
14	36	5	Hypochromic	Achlorhydria	Poor	35	3.22	74	4.92	66	No therapy	16	..	None
15	34	1	Hypochromic	Achlorhydria	Poor	34	2.87	65	4.09	35	No therapy	None
16	34	8	Hypochromic	Achlorhydria	Poor	38	3.29	80	4.95	55	†
17	26	4	Hypochromic	Achlorhydria	Poor	32	3.31	72	4.73	72	No therapy	17	..	None
18	31	6	Hypochromic	Hypochlorhydria	Poor	27	2.12	†
19	41	15	Hypochromic	Hypochlorhydria	Poor	44	3.96	70	4.18	86	No therapy	43	..	None
20	29	5	Hypochromic	Hypochlorhydria	Poor	25	3.56	83	4.93	66	Liver extract	18	..	None
21	21	1	Hypochromic	Hypochlorhydria	Poor	43	3.20	76	4.18	38	Liver extract	10	..	None
22	40	4	Hypochromic	Hypochlorhydria	Poor	40	3.87	80	4.71	75	No therapy	98	..	None
23	32	7	Hypochromic	Hypochlorhydria	Poor	39	4.73	93	6.39	62	Liver extract	18	..	None
24	39	8	Hypochromic	Hypochlorhydria	Poor	33	3.03	88	5.26	50	No therapy	100	..	None
25	35	9	Hypochromic	Hypochlorhydria	Poor	44	4.42	70	4.54	100	No therapy	37	..	None
26	28	2	Hypochromic	Hypochlorhydria	Poor	41	4.04	90	4.96	96	No therapy	6	..	None
27	27	3	Hypochromic	Hypochlorhydria	Good	30	3.24	90	4.96	96	No therapy	12	..	None
28	37	8	Hypochromic	Normal acidity	Poor	43	3.83	83	5.33	80	No therapy	†
29	30	7	Hypochromic	Normal acidity	Poor	43	4.23	83	5.33	80	No therapy	†
30	39	11	Hypochromic	Not examined	Poor	36	2.84	No therapy	†
31	30	4	Macrocytic	Achlorhydria	Poor	50	1.87	80	3.87	52	No therapy	52
32	34	7	Macrocytic	Achlorhydria	Good	45	1.98	84	3.80	37	No therapy	21
33	18	1	Macrocytic	Normal acidity	Poor	57	2.50	84	3.80	37	No therapy	12	..	†
34	32	6	Macrocytic	Hypochlorhydria	Poor	37	1.64	84	3.80	37	†
35	44	7	Macrocytic	Hypochlorhydria	Poor	20	1.05	84	3.80	37	†
36	39	10	Macrocytic	Hypochlorhydria	Poor	27	1.35	84	3.80	37	†

* Patient previously reported, reference (4).

† Patient not treated.

§ Liver extract No. 343, derived from 400 gm. liver, given.

‡ Patient treated during the course of pregnancy.

** See text for details of treatment.

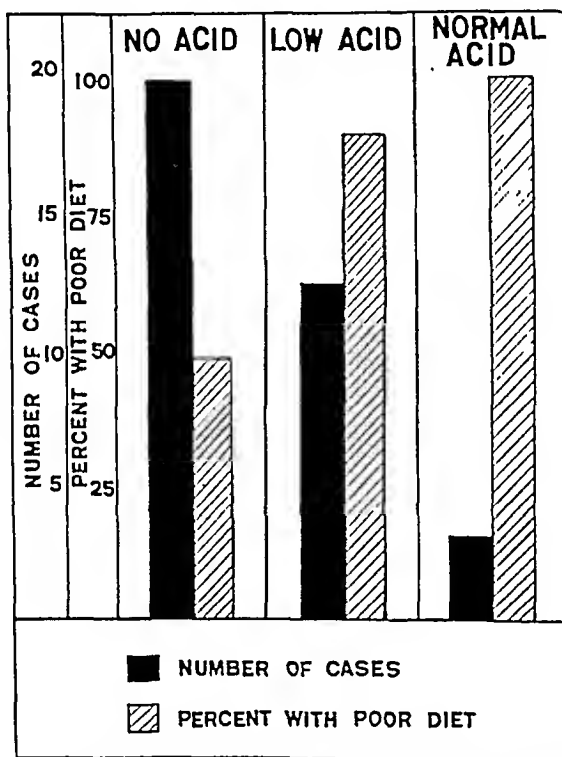
fact that 4 patients developed severe complications, from which 2 died.

The 36 patients considered in this study were selected only after a critical search had eliminated the possibility of blood loss, infection or other complications being present. Detailed histories of the patients' diets over a period of years, as well as during pregnancy, were taken. The state of the gastric secretions was evaluated by routine gastric analyses as previously described.^{1,2} Blood examinations were made of the infants born to these patients whenever possible.

Results. Blood Picture. Morphologic study of the blood showed that 30 of the 36 patients had anemia of the hypochromic (chlorotic, microcytic) type, with marked reduction in hemoglobin and less marked reduction of erythrocytes (Table 1). Leukocytes were normal or increased, as were the blood platelets. No abnormalities of the differential white blood cell counts were noted except that the polymorphonuclear neutrophils were frequently increased when the total leukocyte count was elevated. Icteric indices were normal. The erythrocytes were small and deficient in hemoglobin when studied on stained smear. Moderate variation in size and shape was noted, but true microcytes or macrocytes were not observed, nor were oval or tailed forms seen. This was corroborated by the determination of the mean corpuscular volume and hemoglobin concentration⁵ in a number of cases. The average of the erythrocyte count of these 30 patients when first observed was 3,359,000 cells per c.mm. (range, 2,120,000 to 4,830,000) and the average hemoglobin (Sahli), 35 per cent (range, 25 to 44 per cent) (100 per cent hemoglobin = 15.6 gm. per 100 cc. of blood). The blood picture of these 30 patients, then, corresponded in every detail to that of the blood as noted in the early descriptions of chlorosis and as recently described as simple achlorhydric anemia,⁶ hypochromic anemia with achlorhydria,⁷ idiopathic hypochromic anemia⁸ and chlorotic anemia with achlorhydria.⁹ Its features are those of an anemia mainly due to defective blood formation.

Six of the 36 patients had anemia of the macrocytic (hyperchromic, pernicious) type. In these women the numbers of erythrocytes were more markedly diminished than the amount of hemoglobin, with a resultant color index above 1 (Table 1). Blood platelets and leukocytes were normal or diminished in numbers. Icteric indices were either normal or slightly increased. On smear, the erythrocytes showed moderate variation in size and shape with macrocytes, microcytes and occasional oval and tailed forms. The cells appeared well filled with hemoglobin. Mean corpuscular volume determinations showed an increased cell size (105 to 130 cubic micra) but not so marked as is frequently seen in true pernicious anemia. In general, then, these patients had a blood picture simulating that seen in typical Addisonian pernicious anemia and

conforming in every respect to the description given of the pernicious anemia of pregnancy.^{10,11,12,13} This condition differs from Addisonian pernicious anemia by virtue of its occurrence in association with pregnancy or the puerperium and the absence of relapse, although all specific therapy be omitted, following recovery. In common with pernicious anemia, the blood picture is suggestive of an anemia mainly due to defective blood formation. Furthermore, achylia gastrica is not found as uniformly as in Addisonian pernicious anemia, only 2 of the 6 women reported here having this condition. It is of interest that 1 of these 2 women had normal gastric acidity when reexamined 2 years later. A subsequent pregnancy was not complicated by macrocytic anemia, although marked gastric hypoacidity occurred during the course of this pregnancy.



ANALYSIS OF 34 PATIENTS WITH HGB UNDER 45%

CHART I.—Gastric acidity and diet of 34 patients with severe anemia of pregnancy.

Gastric Analyses. The results of gastric analyses following histamin stimulation are graphically shown in Chart I. More than half of the total number, 19 patients, were unable to secrete free hydrochloric acid. A third more of the patients secreted little or no acid following alcohol test meals and subnormal amounts following the injection of histamin. Three patients only secreted a normal amount of hydrochloric acid. It is to be noted that the observations recorded in Table 1 and Chart I are postpartum. A

number of those patients who had low acidity after parturition had had complete anacidity during pregnancy. Four of the 6 patients with macrocytic anemia had free acid in the gastric contents and a fifth was found to have free acid 2 years later.

Over two-thirds of the patients of this series had definitely unsatisfactory diets during pregnancy and frequently prior to it (Table 1). Chart I, however, shows that half of the patients with anacidity had good diets, suggesting that achlorhydria alone or a state associated with it is capable of conditioning a deficiency of blood-building materials. The obvious and characteristic features of the poor diets were the low intake of iron and of proteins other than milk. The almost complete absence of meat proteins from the

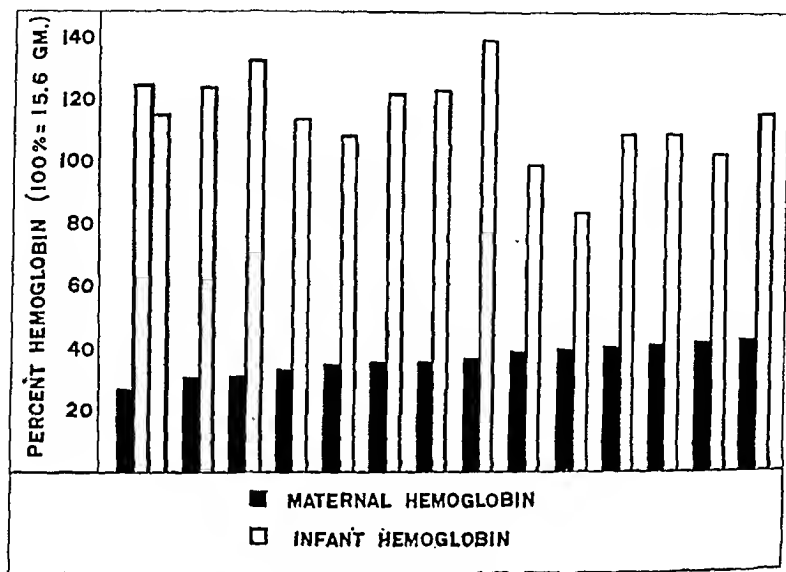


CHART II.—Comparison of infant and maternal hemoglobin in severe anemia of pregnancy.

diet was particularly noted in the patients with macrocytic anemia. No evidence of deficiency of fat, carbohydrate or total calories was observed in any of the diets. With the low protein intake of some of the patients there was probably also a low intake of vitamin B₂. A characteristic "poor" diet consisted of toast, butter, coffee, milk and sugar for breakfast; bread, butter, potato or rice, pastry or cake, tea, milk and sugar for dinner; and cereal, milk, bread and butter for supper; with fruit, meat and vegetables once or twice a week. The "good" diets included fruit, meat and vegetables 4 or more times a week, although many of the diets classified as good could not be considered optimal.

Blood Examinations of Infants. Examination was made of blood obtained from a freely bleeding puncture of the heel of 14 of the

infants born to the women who had been untreated during pregnancy. The results (Chart II) show that *no matter how anemic the mother, the infant is born with a normal amount of hemoglobin*. The blood of these infants was identical in every respect to the blood of a similar group of infants born of mothers not anemic. All infant blood examinations were made during the first few days after birth since there is normally a rapid decrease in hemoglobin and erythrocytes in the first weeks of life.¹⁴

These data, then, indicate that all of these patients had either a direct dietary deficiency or a disturbance of gastric secretion or, in many cases, a combination of both these factors. In addition, since the building materials used in the formation of the fetal blood are derived by necessity from the maternal organism, a condition analogous to chronic blood loss was uniformly present in all the patients.

Experimental Observations. In an endeavor to determine the exact nature of the deficiency and to correlate these observations with the two types of blood picture, various substances were administered, as in similar experiments previously performed in cases of idiopathic hypochromic anemia¹⁵ and in Addisonian pernicious (macrocytic) anemia.^{16,17,18,19,20}

Hypochromic Anemia. Control periods without therapy of from 6 days to 6 months were maintained in 16 of the 30 cases that had anemia of the hypochromic type. No significant reticulocyte responses or gains in hemoglobin or erythrocytes were observed. Three patients were given liver extract No. 343 (N. N. R.), derived from 600 gm. of liver daily. Small reticulocyte responses occurred in 2, but no significant gain in either hemoglobin or red blood cells was observed. Twenty-three patients, during or after pregnancy, were given 6 gm. of ferrie ammonium citrate daily. In every case prompt reticulocyte responses and an average gain of 0.65 per cent (0.1 gm. per 100 cc.) hemoglobin per day occurred, together with rapid clinical improvement (Table 1, Chart III). In none of these cases was there any change made in the diet during the period of observation. However, in certain other patients, not included among the 30, diets rich in iron produced a slow remission of the anemia.

These observations suggest that the hypochromic anemia of pregnancy, like idiopathic hypochromic anemia, is due to a deficiency state correctable by iron therapy and either conditioned by abnormalities of the gastrointestinal tract or by a direct lack of iron in the diet. In addition, an analogy may be made between the blood requirements of the fetus and chronic blood loss associated with certain cases of idiopathic hypochromic anemia.

Macrocytic (Pernicious) Anemia. Of the 6 patients who had a blood picture practically indistinguishable from that of Addisonian pernicious anemia, the 2 with the least anemia were observed after parturition during control periods without therapy for 12 and 21 days, respectively, in which no improvement occurred. Imme-

diately thereafter, however, prompt reticulocyte responses appeared in each case, together with a gain of hemoglobin and erythrocytes following the daily administration of 6 gm. of ferric ammonium citrate. Clinical improvement, with a gain in appetite, likewise occurred so that these 2 patients, although receiving the same type of diet as before, began to eat much larger quantities of food, including meat. The data presented below suggest that this change in the diet of these 2 patients was of importance in the remission of the anemia. A third patient was given liver extract No. 343 (N. N. R.) derived from 400 gm. of liver daily. An exactly comparable clinical and hematologic response occurred as in the 2 cases mentioned above.

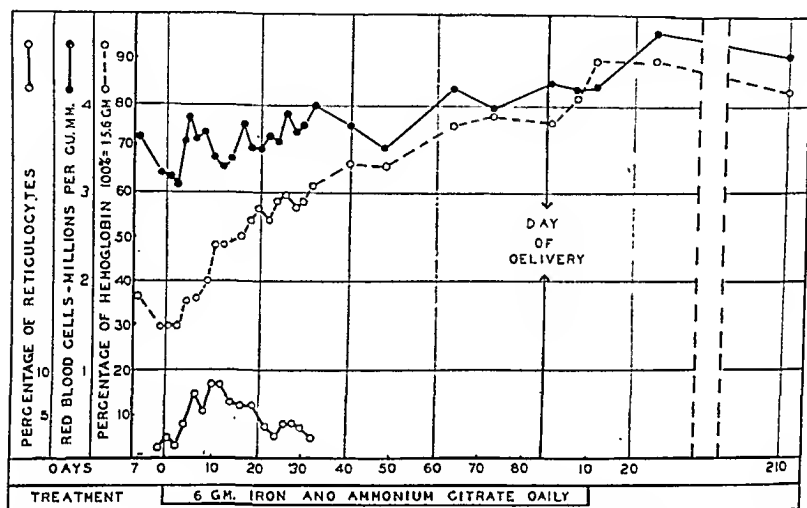


CHART III.—Typical response to iron therapy in hypochromic anemia of pregnancy.

These observations, together with the reports in the literature of the successful treatment of this macrocytic type anemia in pregnancy with liver extract alone, suggested the possibility that there might be a combined deficiency of iron and of the substance present in liver, as has been reported in pernicious anemia by Minot and Castle²¹ and Beebe and Lewis.²² To test this hypothesis a fourth patient was given first a small dose of liver extract potent for pernicious anemia which was followed by moderate reticulocyte response. Immediately thereafter iron was administered and produced a second reticulocyte response. During a third period without liver or liver extract the erythrocytes began to decrease. Daily doses of liver extract were then begun again and iron was continued. A third reticulocyte response, together with rapid clinical and hematologic improvement, occurred. It seemed probable, therefore, that an iron deficiency or a state improved by iron therapy brought about

by the same mechanism as in the hypochromic anemia of pregnancy was present at least in certain cases of the macrocytic type of anemia in addition to a deficiency of the type encountered in Addisonian pernicious anemia.

It has been stated²⁰ that any one or more of 3 mechanisms may produce the deficiency causing Addisonian pernicious anemia: (1) A lack of the specific intrinsic factor of the gastric juice, even with an adequate intake of extrinsic substrate found in beef muscle and yeast extracts; (2) a chronic lack of the substrate in the diet even with a normal amount of the intrinsic factor in the gastric juice; (3) a failure of the absorption or utilization of the product of the interaction of intrinsic and extrinsic factors. Accordingly, to determine if any of these mechanisms were involved in the pernicious

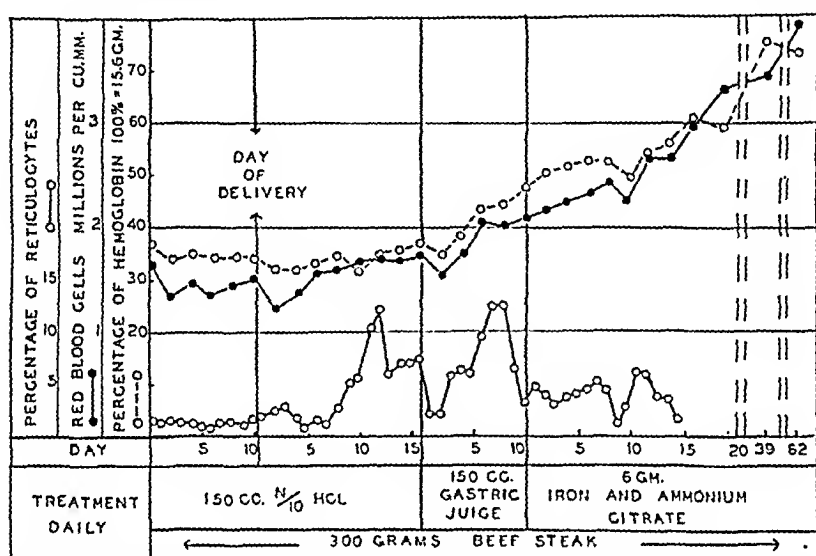


CHART IV.—Response to beef muscle, gastric juice and iron in macrocytic anemia of pregnancy.

anemia of pregnancy, a fifth patient, suffering from this type of anemia, first seen 10 days before delivery, was given successive periods of controlled therapy (Chart IV). First, this patient received daily for 10 days 300 gm. of beefsteak followed by 150 cc. $\frac{N}{10}$ hydrochloric acid. No hematologic response occurred. When, however, following delivery this same therapy was continued, a delayed but definite reticulocyte response occurred, together with a small gain in erythrocytes and hemoglobin in a period of 16 days.

This state of affairs suggests that before delivery the patient lacked the intrinsic factor of the gastric juice and that there was a partial return of the intrinsic factor in the gastric juice soon after delivery. When, next, in place of the hydrochloric acid, a like amount of normal human gastric juice was administered with the beef muscle there occurred a prompt second response of reticulocytes, together

with a gain of 0.5 million red blood cells in 10 days. This certainly suggests that the normal human gastric juice supplied something which had not previously been present in adequate amounts and which was not hydrochloric acid. Iron was then given, resulting in a small tertiary reticulocyte response and further improvement in her blood, suggesting in addition, as in the other cases of this type, a deficiency state which could be favorably affected by iron. It may be argued that the first reticulocyte response was in the nature of a "spontaneous" remission unrelated to the state of the gastric juice, despite the fact that in the control period of other cases without therapy after parturition, there was no evidence of remission. If this were the case, it is at least a remarkable coincidence that the second reticulocyte response was caused by the administration of intrinsic factor in the form of normal human gastric juice.

A sixth patient, first seen 18 days after parturition, was given 300 gm. of beefsteak daily followed at once by 150 cc. of $\frac{N}{10}$ hydrochloric acid for 10 days with no response of reticulocytes or mature red blood cells. Thereafter, 150 cc. of normal human gastric juice was substituted for the $\frac{N}{10}$ hydrochloric acid; this resulted in a small reticulocyte response. Iron was then administered in addition to the above therapy with a resultant second small reticulocyte response. At this point a transfusion of blood was given. Iron and beefsteak were continued, but gastric juice omitted. No response of reticulocytes or of mature erythrocytes followed. Gastric juice was resumed and a third small reticulocyte response occurred. Liver extract No. 343 (N. N. R.) was then administered, resulting in a reticulocyte response of 46 per cent at its peak, and rapid hematologic and clinical improvement. This case serves to illustrate the absence of any effect from transfusion of blood other than a temporary elevation of the red blood cells and hemoglobin, as well as the definitely positive effect of the mixture of beefsteak and normal gastric juice. The failure of the latter to give a more marked effect may best be explained on the basis that this mixture supplied a lesser amount of the necessary substance than did the dose of liver extract potent for pernicious anemia.

[In further confirmation of the above are observations made on 2 additional patients with macrocytic anemia of pregnancy who were studied since this manuscript was submitted. After control periods of 8 and 23 days respectively following delivery, during which no change occurred, each was given daily 16 gm. of autolyzed yeast (Vegex) rich in vitamin B₁₂. The first patient had a small reticulocyte response but no gain in erythrocytes during several weeks until normal gastric juice was administered with the autolyzed yeast, when a second and larger reticulocyte response occurred together with a prompt rise of erythrocytes. The second patient had a maximum reticulocyte response and rapid gain in erythrocytes under autolyzed yeast therapy alone. The first patient is entirely analogous to the fifth patient mentioned above, and the second patient illustrates that after delivery, when these observations were made, there was solely an extrinsic factor lack.]

These observations suggest that the macrocytic anemia of pregnancy, like other macrocytic anemias responding to liver extract, is due to a deficiency state brought about either by a direct lack of an extrinsic factor (vitamin B₁₂) in the diet or by a lack of an intrinsic factor of the gastric juice. In addition, a concomitant deficiency state corresponding to that observed in the hypochromic anemia of pregnancy is frequently present.

Discussion. The voluminous literature devoted to the consideration of anemia in pregnancy (see preceding paper²) emphasizes two possible etiologic factors: (1) A toxic substance elaborated by the product of conception which inhibits bone-marrow activity; (2) a hemolytic agent formed by the product of conception (usually stated to be a syncytial hemolysin) which destroys the maternal blood corpuscles. However, no evidence has been produced in proof of either of these theories, and the data presented in this and the preceding paper of this series do not support them, because comparable responses to therapy were obtained either during or after pregnancy and no responses occurred as a result of delivery alone.

In 1930⁴ evidence drawn from 3 of the cases presented here was advanced in favor of the theory that the hypochromic anemia of pregnancy was due to a deficiency of blood-building materials brought about by gastric anacidity (or a defect associated with it), in the presence of fetal blood requirements. The data presented here, previously published in abstract,^{24,25} indicate that in addition to such indirect deficiency "conditioned" by gastrointestinal defects, certain cases are due to a direct lack of blood-building materials in the diet, and others to a combination of direct dietary deficits and gastrointestinal defects.

The hypochromic anemia of pregnancy, then, is entirely analogous to idiopathic hypochromic anemia in that the etiologic mechanisms apparently responsible for its occurrence—direct dietary deficiency or indirect dietary deficiency conditioned by gastric anacidity and hypoacidity or a factor associated with these defects, and fetal blood requirement (which has the same effect as chronic blood loss in cases of idiopathic hypochromic anemia)—are apparently identical with the mechanisms operating in the production of idiopathic hypochromic anemia. Iron therapy is equally efficacious in the treatment of both conditions.

It may be thought that the number of observations made upon the macrocytic anemia of pregnancy is too limited to warrant discussion. However, the many similar experiments^{16,17,18,19,20} performed upon patients with Addisonian pernicious anemia appear relevant to this problem and may serve as controls. That there is often a double deficiency present in this condition in pregnancy seems apparent, and it is known that this is not infrequently demon-

strable in pernicious anemia,^{22,23} although usually only liver or liver extract need be given therapeutically. In Addisonian pernicious anemia there is ordinarily a permanent lack of the specific "intrinsic factor" from the gastric juice, which makes it necessary to supply the deficiency indefinitely. Cases have, of course, maintained normal blood conditions over long periods of time without liver or allied therapy, suggesting that occasionally there is a return of the specific gastric intrinsic factor, and, indeed, such a return has actually been demonstrated in 1 case of macrocytic anemia.¹⁹ The observations reported here on the inefficacy of beefsteak alone during the progress of pregnancy suggest the lack of this specific gastric factor at that time. The moderate responses obtained with beefsteak alone following delivery suggest a return of this factor, although the more marked responses obtained when normal human gastric juice was administered in addition to the beefsteak, indicate that complete return had not yet occurred. That complete restoration does eventually take place is suggested by the fact that it has often been observed that these individuals do not relapse when once completely well following delivery.

The demonstration of the lack of intrinsic factor in these 2 cases of pernicious anemia of pregnancy must not be considered as evidence that this is true for all cases, since it is perfectly possible that, as has been suggested for Addisonian pernicious anemia,^{19,20} cases may be discovered in which the lack of the extrinsic factor of the diet alone may be responsible for the anemia. Indeed, the cases reported by Wills²⁶ are probably due to this mechanism. The lack of correlation between the presence or absence of free hydrochloric acid in the gastric secretions and the presence or absence of the intrinsic factor need not be considered adverse to the hypothesis, since this lack of correlation has been demonstrated in Addisonian pernicious anemia.¹⁹ That the acid alone is not involved is evidenced by the absence of response when acid was administered with the beefsteak.

These observations, then, indicate the analogous mechanisms involved in the production of the macrocytic anemia of pregnancy and Addisonian pernicious anemia, and indicate the efficacy of similar therapy in the two conditions. Likewise, similar mechanisms are indicated for the hypochromic anemia of pregnancy and idiopathic hypochromic anemia, and iron is found to be equally efficacious in alleviating either condition.

Conclusions. 1. The hypochromic anemia of pregnancy is due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of the fetal demand for blood-building materials, and may be completely relieved, either during or after pregnancy, by the administration of iron in large doses.

2. The macrocytic anemia of pregnancy is presumably due to a temporary lack in the gastric juice of the specific intrinsic factor which has been shown to be absent from the gastric juice of patients with Addisonian pernicious anemia in relapse. The ultimate complete return of this factor after delivery is hypothesized. It is believed that the lack of the extrinsic factor (vitamin B₂) from the diet may produce similar effects. The macrocytic anemia of pregnancy ordinarily may be completely relieved with liver extract, although iron is sometimes required in addition.

3. The similarity of the etiologic mechanisms involved in the hypochromic anemia of pregnancy and idiopathic hypochromic anemia, and in the macrocytic anemia of pregnancy and Addisonian pernicious anemia is pointed out.

4. Anemia in pregnancy does not cause any lowering of the infant hemoglobin or erythrocyte count at birth.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose coöperation this study was made possible. The technical work on the blood was chiefly performed by Miss Margaret Evans and Miss Charlotte Nicklin.

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AGRANULOCYTIC ANGINA (PERNICIOUS LEUKOPENIA).

A STUDY BASED ON 18 CASES WITH 9 NECROPSIES.

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THE concept of agranulocytic angina as a disease entity, rather than as a mere hematologic manifestation of various unrelated disorders, is still open to question. The opinion herein entertained is that agranulocytic angina exists as a valid clinicopathologic entity in the same sense that pernicious anemia is accepted as such. Not many years ago it was difficult to defend the nosologic purity of pernicious anemia. Today, with a practically specific therapeutic test for this disease in its relapse phases, one may confidently assert that a given individual has pernicious anemia even though there may be present an associated morbid process capable, in itself, of producing anemia.¹ In the light of this therapeutic test it is becoming apparent that certain conditions, which were formerly regarded as simulating pernicious anemia, may be actually contributing causes of the disease itself (sprue, fish tapeworm infestation, gastrointestinal carcinoma, etc.). It is now possible to exclude certain obscure pernicious-like anemias from the category of pernicious anemia by virtue of their failure to respond to adequate specific therapy. In a similar way, we believe, agranulocytic angina should be viewed as a disease entity which awaits the discovery of a specific therapy to stamp it with unmistakable validity.

The purpose of this report is to summarize the significant data of 18 cases of this disease studied in the hospital of the University of Pennsylvania since 1927. Prior to this date, our clinic failed to recognize the condition as such.² Of the 18 cases included in this report we have had personal contact with all but 2. Several (Cases 5,² 10³ and 11⁴) have been previously reported by ourselves or others and 1 case (Case 8⁵) will be made the subject of a separate communication.

A summary of certain items of clinical importance is presented in Table 1. Cases 1 to 13, inclusive, are classical instances of

agranulocytic agina (pernicious leukopenia) about which no reasonable doubt can be raised. Cases 14 to 18 are, in our opinion, also examples of this disease, with certain atypical manifestations which are enumerated below.

TABLE 1.—SUMMARY OF CLINICAL DATA.

Case No.	Age.	Sex.	Race.	Previous attacks.	Duration of attacks.	Duration of remission.	Duration of life after onset.	Outcome.	Classification.
1 (Miss A.)	19	F	W	None	4 dys.	None	4 dys.	Dead	Acute
2 (Mr. J. C.)	78	M	W	None	3 wks.	None	3 wks.	Dead	Acute
3 (Mrs. C.)	68	F	W	Uncertain	Uncertain (chronic)	Uncertain	4 yrs.	Alive	Chr. contin.
4 (Mr. D.)	56	M	W	None	1 wk.	None	1 wk.	Dead	Acute
5 (Mrs. F.)	48	F	W	None	1 wk.	None	1 wk.	Dead	Acute
6 (Mrs. L.)	31	F	W	None	10 dys.	None	10 dys.	Dead	Acute
7 (Mr. W.)	68	M	W	None	5 dys.	None	5 dys.	Dead	Acute
8 (Mrs. S.)	42	F	W	Five	3-6 wks.	3 wks. to 18 mos.	2½ yrs.	Alive	Chr. remit.
9 (Mr. E. S.)	22	M	W	None	5 dys.	None	5 dys.	Dead	Acute
10 (Miss S.)	26	F	W	None	2-3 wks.	3 yrs.	3 yrs.	Alive	Acute
11 (Mrs. L. S.)	58	F	W	Probably several	1-2 wks.	6-12 mos.	1 yr.	Dead	Acute*
12 (Mr. W.)	42	M	W	None(?)	2-3 wks.	None	2-3 wks.	Dead	Acute*
13 (Mr. M. W.)	52	M	W	None	3 days	None	3 dys.	Dead	Acute
14 (Mr. B.)	41	M	W	None(?)	(?)	Incompl.	2 yrs.	Dead	Chr. contin.?
15 (Mr. J. B.)	64	M	W	None	10 mos.	None	10 mos.	Dead	Chr. contin.
16 (Dr. R.)	42	M	W	None	5 mos.	Incompl.	5 mos.	Dead	Chr. contin.
17 (Mr. W. W.)	19	M	W	None	4½ mos.	None	4½ mos.	Dead	Chr. contin.
18 (Mr. K.)	54	M	W	Probably 5	1-2 wks.	2 wks. to 6 mos.	2 yrs.	Alive	Chr. remit.

* Uncertain history of prior attack.

CASE 14 (Mr. B.) had splenomegaly of sufficient magnitude to raise the question of "Banti's disease," Hodgkin's disease or of leukopenic leukemia. Against Banti's syndrome are the absence of demonstrable hepatic disturbances and the magnitude of the leukopenia (Table 2). Against leukemia and Hodgkin's disease are the absence of lymph node enlargements, and the presence of rectal and oropharyngeal lesions with profound granulocytopenia. This patient died with a terminal hemorrhage from the upper digestive tract, probably due to agranulocytic ulceration of the esophagus.

CASE 15 (Mr. B.) was complicated by the presence of carcinoma of the prostate with Roentgen ray evidence of possible spinal metastasis, but without other demonstrable bone marrow metastases at necropsy.

CASE 16 (Dr. R.) exhibited a moderate hyperchromic anemia (Table 2) which responded to massive liver therapy by a 10 per cent reticulocytosis and subsequent recovery from anemia. This response is suggestive of pernicious anemia, but the presence of free hydrochloric acid in the gastric analysis is against pernicious anemia. Furthermore, in spite of "erythron" recovery, this patient remained in a state of profound granulocytopenia, and his sluggish rectal ulcer never healed. These facts support the diagnosis of agranulocytic angina (rather than pernicious anemia, aplastic anemia, etc.). He died in another hospital, after 5 months illness, with a terminal leukocyte count of 450 per c.mm. (all lymphocytes) and a normal red cell and hemoglobin content.

CASE 17 (Mr. W.) is unusual in the fact that absolute mononucleosis was marked at the onset and again before death some months later. Careful hematologic examination during life and necropsy study of the spleen, liver and bone marrow altogether excluded monocytic and lymphatic leukemia as diagnostic possibilities. The case was otherwise a typical one

of agranulocytic angina with oropharyngeal and rectal lesions, and marked granulocytopenia.

CASE 18 (Mr. K.) is listed in the atypical group because we have not had opportunity of studying the patient during a relapse. His history and the leukocyte counts made during attacks and reported to us by the patient's wife (who is a physician) are practically diagnostic.

In the statistics which follow we shall include all of these cases as valid examples of agranulocytic angina. We have not included cases of acute benzene poisoning (1 seen with a terminal white blood count of 500 per c.mm., all lymphocytes), cases of acute arsphenamin poisoning with panmyelophthisic anemia, overwhelming septicemia with terminal leukopenia, cases of "idiopathic" aplastic anemia, cases of leukopenic leukemia and leukopenic Hodgkin's disease, cases of obscure anemia with leukopenia or cases of profound leukopenia from Roentgen ray.

The patient with the longest duration of life (Case 3) is in a chronic granulocytopenic status complicated by auricular fibrillation (now 4 years since onset). Case 10 has remained perfectly well, both clinically and hematologically, for 3 years since her violent attack.³ Of the 11 cases (61 per cent) classified as acute only 1 is living (Case 10). The mortality in this "acute" group is over 90 per cent. Five cases (28 per cent) are classified as chronic continuous. Of these, 1 is alive (Case 3). Two cases are of the chronic remittent type (Cases 8 and 18). Both of these are alive and 1 of the latter is apparently cured (Case 8). Of the entire group of 18 cases, 14 are dead (78 per cent mortality), 2 are cured (in the sense that they have remained clinically and hematologically normal for 18 months and 3 years, respectively), and 2 are living but are either chronically granulocytopenic or are subject to frequent recurrent attacks of the disease.

The onset symptoms recorded in our cases are weakness and fatigue (100 per cent), malaise and feverishness (100 per cent), sore throat (79 per cent), sore mouth (47 per cent), cough (34 per cent), chills (34 per cent), vomiting (26 per cent), rectal distress (18 per cent), dysphagia (10 per cent). Significant physical findings are fever (100 per cent), oropharyngeal lesions (84 per cent), rectal or vaginal lesions (44 per cent), dental sepsis (44 per cent), slight cervical adenopathy (36 per cent), jaundice (18 per cent), moderate splenomegaly (18 per cent) (extending 1 inch or more below costal margin) and barely palpable spleens (10 per cent). A few petechiæ were noted in 1 of the patients, rectal ulcer bleeding in 2 and epistaxis in 1. This latter individual suffered a terminal hematemesis, presumably from esophageal ulceration. Although weakness and fatigue are most common symptoms, we have not been as impressed with their outstanding significance as have certain other observers.⁶ We have seen patients with this disease (as well as patients with leukemia and other diseases) whose total

granulocytes have varied from zero to supernormal numbers without any other symptomatic or objective change of status.

TABLE 2.—LEUKOCYTES, RED CELLS, AND HEMOGLOBIN DURING ACUTE PHASE OF THE DISEASE.

Case No.	White blood cells.			Neutrophils.			Red blood cells.			Hemoglobin.			Classification.
	H.	L.	M.	H.	L.	M.	H.	L.	M.	H.	L.	M.	
1	500	200	300	0	0	0	4.5	4.5	4.5	90	90	90	Acute
2	2,100	1,200	1,500	16	0	6	3.9	3.1	3.7	65	57	60	Acute
3	7,500	1,100	2,000	18	0	9	3.6	3.2	3.4	74	43	60	Chr. contin.
4	1,200	500	800	0	0	0	4.4	3.3	4.0	85	60	70	Acute
5	600	500	500	0	0	0	4.4	4.4	4.4	82	82	82	Acute
6	1,000	800	900	0	0	0	4.8	4.6	4.7	98	90	95	Acute
7	1,250	50	600	0	0	0	4.6	4.6	4.6	85	85	85	Acute
8	4,000	250	1,800	14	0	8	5.0	4.5	4.8	98	87	94	Chr. remit.
9	1,200	500	1,000	0	0	0	4.0	4.0	4.0	70	70	70	Acute
10	3,400	600	1,500	8	0	6	4.8	3.2	4.0	98	62	80	Acute
11	1,000	200	600	0	0	0	4.8	4.3	4.6	98	90	95	Acute
12	6,500	900	1,300	83	26	30	5.2	4.5	5.0	98	83	90	Acute
13	500	500	500	0	0	0	3.5	3.5	3.5	80	80	80	Acute
14	3,800	700	1,300	34	0	20	4.5	3.7	4.0	88	72	80	Chr. contin.
15	3,200	1,900	2,400	16	0	5	4.5	2.6	3.5	95	51	80	Chr. contin.
16	3,200	450	1,500	40	0	20	4.3	2.5	3.8	85	68	75	Chr. contin.
17	16,300	1,500	2,000	33	0	55	4.6	2.4	3.5	90	37	65	Chr. contin.
18	2,500	1,600	2,000	?	?	?	5.0	5.0	5.0	100	100	100	Chr. remit.

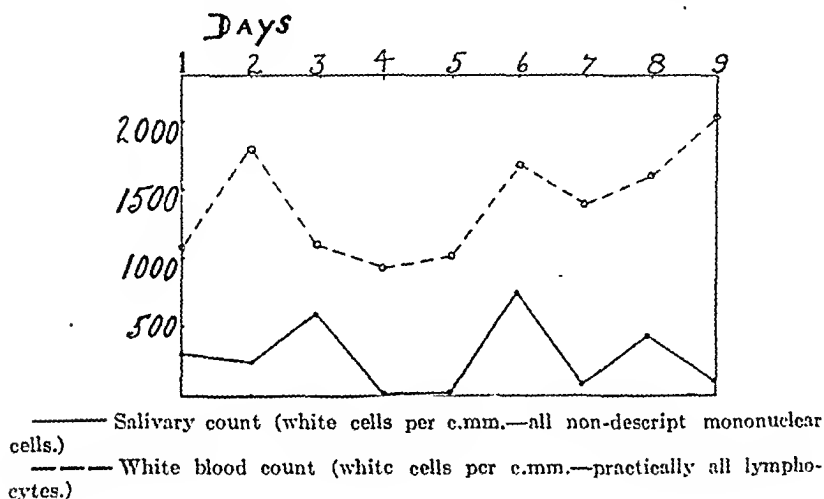
H = High. L = Low. M = Mean.

It is noteworthy (Table 2) that all but 2 patients exhibited complete absence of neutrophils at some stage of the disease. One of these 2 (Case 12) developed bronchopneumonia prior to the first blood count, and subsequently died of bronchopneumonia after hematologic remission had become established. In the other case (Case 18) data concerning the differential count during relapses are not available. The high total leukocyte count before death in Case 17 is unusual in that this represents an absolute increase in monocytes and lymphocytes (only 2 per cent of 16,300 white cells being neutrophils). We have no explanation for this, and none was found at necropsy, *i. e.*, no evidence of leukemia. The nearest approach to this granulocytopenic mononucleosis blood picture in our series is exhibited by Case 3, in whom only 18 per cent of 7500 white cells were neutrophils at one stage of the disease. Of the 18 cases, 13 showed leukopenia of less than 1000 cells. The lowest total leukocyte count (Case 7, 6 hours before death) was approximately 50 cells per c.mm. (personally enumerated and verified by us on two separate counts, each showing only 1 to 2 leukocytes in the entire ruled area of the counting chamber).

The mean red cell count and hemoglobin percentage (Sahli) in our series are 4,100,000 and 75 per cent, respectively. The only cases of red cell counts below 3,000,000 are in individuals with fairly obvious anemia-producing conditions: Case 15, with carcinoma of the prostate and bladder; Case 16, with bleeding hemorrhoids and fissure *in ano*; Case 17, with bleeding rectal ulcer. It is, perhaps, significant that the average of the lowest red cell counts

in the chronic cases is 3,000,000, and in the acute cases is 4,000,000, suggesting the importance of the time factor in the production of anemia in this disease. Although not included in Table 2, no significant pathologic variations in eosinophil, basophil and myelocyte cells were observed except their absence. During the few recovery phases we have never observed the myelocyte crisis recently described by Doan.⁷ In the chronic continuous type we have been impressed by the observation that many of the few remaining neutrophils seen day after day in the blood spreads are nonfilament forms. We have been unable to adduce evidence of excessive peripheral leukocyte destruction, *i. e.*, no undue number of "smudge cells" or of excessive leukocyte fragility in this disease. Study of salivary leukocyte content in 3 cases yielded no consistent results except that in all instances the cells in the saliva were

CHART I.—RELATION OF WHITE BLOOD COUNT TO SALIVARY COUNT IN CASE 14.



nondescript mononuclears with no definite polymorphonuclear neutrophils discernible. For example, in Case 17 salivary counts ranged between 15 and 500 cells per c.mm. during several successive days, while the white blood count was fairly constant at about 4000 cells per c.mm. In Case 13 salivary white counts ranged from 15,000 to 31,000 per c.mm. while the white blood count was 500 cells per c.mm. (all lymphocytes). This might suggest an inverse relationship (Isaacs), but opposed to such interpretation is our observation that an artificially induced leukocytosis (adrenalin) is associated with an increase in the salivary leukocytes. Furthermore, salivary leukocytes in a chronic case of the disease (Case 14) whose blood count was stabilized at 1000 to 2000 white blood cells per c.mm. during a week of observation ranged from 10 to 900 (Chart I).

TABLE 3.—MISCELLANEOUS LABORATORY DATA.

Case No.	Blood type.	Platelets (thou. per c.mm.).	Reticulocytes (per cent).	B.* and C. time.	C.R.†	Blood culture.	B.W.R.‡	Sed. rate.	Miscellaneous.
1	..	(Nor. smear)	1.0	Neg.			
2	A	Neg.			
3	..	180	Neg.			
4	O	281	0.2	Hem. strep.	Neg.		
5	Type III pneumo.			
6	O	112	Neg.			
7	Neg.			
8	A	67 to 250	0.3	Nor.	Nor.	Neg.	Neg.	Neg.	
9	B	294	0.1	Gram + coccus	Neg.		
10	O	107	0.1	Neg.	Neg.		
11	..	256	0.2	Nor.	Nor.	Neg.	Neg.		
12	A	151	...	Nor.	Sl. in 4 hrs.	...	Neg.	Nor.	
13	Nonhem. strep.			
14	..	52 to 150	1.3	Nor.	Nor.	Much incr.	Paul's heterophil antibody test neg.; D'Amato's hemoclastic crisis with 0.001 mg. old tuberculin neg. for tuberculosis.
15	..	200	Neg.	Neg.		
16	A	152 to 250	1 to 10	Nor.	Nor.	Neg.	Neg.	Mod. incr.	Paul's heterophil antibody test negative.
17	O	246	1.2	Nor.	Nor.	Hem. S. aureus	Neg.	Much incr.	
18	..	326	2.2	Nor.	Nor.	...	Neg.	..	Paul's heterophil antibody test negative.

* B. and C. time = Bleeding and clotting time.

† C.R. = Clot retraction.

‡ B.W.R. = Blood Wassermann reaction.

From Table 3 it is clear that marked thrombocytopenia is not common in this disease. Only 2 of our series exhibited less than 100,000 platelets per c.mm. (Cases 8 and 14). Other coagulation factors are normal. The finding of a normal sedimentation rate in Case 12 was so bizarre that the test was repeated and checked several times, with the same result. How a nearly moribund, highly febrile patient could exhibit a normal sedimentation rate has remained a mystery to us. His coagulation time, blood calcium and fibrinogen were all "normal." Further experiments are planned in this connection.

A review of our case histories* shows that the onset of the disease seemed to follow closely on the extraction of teeth in 4 instances (Cases 6, 10, 12 and 18). Eight of our patients gave no history of surgical or other trauma preceding the onset of angina (Cases 1, 2, 5, 7, 8, 11, 13 and 15). In 1 patient (Case 3) an acute gall bladder attack seems to have initiated the disease; in another (Case 9) an

* Owing to lack of space and because the essential data are presented in the tables the case histories have had to be omitted by the Editors.

intravenous injection of orthiodoxy-benzoate and in another (Case 4) the surgical removal, under spinal anesthesia, of an old osteomyelitic sequestrum. Two of our patients had taken quinin intermittently during their lives (for supposed malaria). One was given diphtheria antitoxin, but the disease was probably already underway at this time. None of our patients presented any convincing evidence of allergic disturbance.

We have records of normal white blood counts and granulocyte percentages prior to the onset of the disease in 8 (Cases 3, 4, 6, 9, 10, 11, 12 and 15). In 2 of these cases we had previously observed a "normal" neutrophilic leukocytosis under appropriate conditions (*e. g.*, Case 10 exhibited a 20,000 white blood cell count with over 80 per cent "polys" after an emergency abdominal operation in 1927; Case 12 had 15,000 leukocytes with 78 per cent polymorphonuclears in 1929, the day after tonsillectomy). These facts make it difficult to uphold the hypothesis of a "constitutional predisposition" to this disease. In none of our cases was there any suggestion of an hereditary or familial or seasonal or contagious incidence of the disease.

TABLE 4.—TREATMENT.

Case No.	No. of transfusions.	No. of "stimulative" Roentgen ray treatments.	No. of grams pentose nucleotid (Jackson) injected.	Injections of purine bases.	"Reticulin" injections.	No. of vials liver extract ("343").	Liver extract (parental) injections.	Fixation abscess (turpentine).	Neosphenamin (intravenous) injections.	Removal of focal infection after onset of disease.	Formic acid injections (subcutaneous) (Dr. C. H. P. Pepper)	Outcome.
1	.	2	Dead
2	.	2	2	Dead
3	.	2	*	..	Alive
4	.	2	*	Dead
5	.	1	*	Dead
6	.	2	3	15	Dead
7	.	..	40	3	Dead
8	.	13	17	..	4	*	..	*	..	Alive
9	.	2	*	Dead
10	.	5	5	100	Alive
11	.	3	18	Dead
12	.	3	..	10	Dead
13	.	1	1	..	1	Dead
14	.	..	140	Dead
15	.	3	3	3	7	90	Dead
16	.	4	..	170	..	200	*	..	Dead
17	.	8	9	420	6	Dead
18	Alive

Additional treatment in all cases included oropharyngeal care, avoidance of drugs that might reasonably produce an anaphylactoid reaction (Dr. Pepper's suggestion), the use of orange juice, "vitavose," calcium gluconate, and cod-liver oil.

TABLE 5.—SIGNIFICANT NECROPSY FINDINGS.

Case No.	Digestive tract.	Genital tract.	Spleen.	Bone marrow.	Miscellaneous.
2. J. C. (Mr. J. C.)	Ulcers in mouth	Normal	170 gm.; many monos and lymphs, no polys	Sternum, ribs, and vertebrae show "congestion" and "no evidence of aplasia"	Myocardial degeneration; right upper lobar pneumonia; no polys in tissue sections.
4. (Mr. D.)	Ulceration and edema of uvula	Normal	250 gm.; acute splenic tumor; many mononuclear leukocytes; no polys	Sternum, ribs, and femur—intense congestion and hyperplasia of myeloid elements but no polys	Cardiac hypertrophy; pulmonary infarct.
5. (Mrs. F.)	Necrosis of tonsils and pharynx; edema and ulceration of larynx	Normal	Moderately enlarged; packed with red cells and mononuclear leukocytes; no polys	Marked red cell hyperplasia; "scarcity of myeloid cells" (femur only, and not examined by us)	In all organs, small necrotic patches without cellular reaction; widespread necrosis of walls of smaller arteries and veins.
6. (Mrs. L.)	Gingival ulceration; large hemorrhagic ulceration of descending colon	Large ulcer of vulva	270 gm.; acute splenic tumor; no polys	Femur and sternum marked myeloid and erythroblastic hyperplasia; no eosinophils or polys	Myocardial degeneration; congestion of lungs; congestion of adrenals and lymph nodes; no polys in sections.
11. (Mrs. L. S.)	Ulcers of mouth	Normal	140 gm.; congested with red cells; many lymphos and monos; no polys	Considerable myelocytic and myeloblastic hyperplasia in femur, tibia, and ribs; no eosinophils or polys	Nearly complete disappearance of lymphoid tissue throughout the body; heart's blood culture pure <i>B. coli</i> communis.
13. (Mr. M. W.)	Ulcers of gums and pharynx	Normal	240 gm.; acute splenic tumor; no polys	Moderate myeloblastic hyperplasia in islands in femur and tibia; other areas fatty	Myocardial and pulmonary congestion; moderate lymph node hyperplasia; acute interstitial focal nephritis.
15. (Mr. J. B.)	Normal	Prostatic Ca.	300 gm.; acute splenic tumor; a few polys	Exhaustion in femur; myeloid hyperplasia in ribs (myelocytes and myeloblasts but no polys)	Enlarged liver; recent lobular pneumonia.
16. (Dr. R.)	Ulcers of lip and gums with necrosis of alveolar process of right mandible	Normal	320 gm.; slight perisplenic and marked chronic congestion; packed with red cells and mononuclear leukocytes; no polys	Sternum and ribs normal red; femur fatty (normal); sternum of practically normal cellularity (except for increased red cell congestion); many myeloblasts and normoblasts but no myelocytes or polys or eosinophils; a few megakaryocytes	Pulmonary infarction; terminal jaundice; liver considerably enlarged (cloudy swelling and fatty infiltration); a few slightly enlarged mediastinal lymph nodes showing inflammatory hyperplasia with many mononuclear leukocytes and macrophages and large lymphocytes but no polys.
17. (Mr. W. W.)	Ulcers in mouth and pharynx; perirectal inflammation; ulcer in rectum	Normal	250 gm.; overgrowth of large monos; no polys	Marked erythropoietic and myeloblastic hyperplasia in femur and tibia; arrest of maturity of myelocytes; no eosinophils or polys	No polys in tissues examined.

Treatment summary is presented in Table 4. Each of our patients, except 4 (Cases 3, 7, 14, 18) received 1 or more blood transfusions. The mortality in this transfusion group was 71 per cent. Pentose nucleotid (Jackson) was administered to 5 patients. One received 2 injections (20 gm. each) and died within 48 hours (Case 7). One received only 1 injection (Case 12), with an ensuing reaction of such alarming character that it was not repeated. This patient also died. Case 14 was given 1 intramuscular and 1 intravenous injection (10 gm. each) every day for 7 days, without any significant change in his chronic granulocytopenic status. He died a few weeks later. Case 16 showed a moderate increase in granulocytes the day after the first of 10 daily injections. This improvement seemed too soon to be attributed to nucleotid. The improvement was subsequently not maintained and a second complete course of this treatment was without effect. This patient reacted violently, with fever up to 104° , from each intramuscular injection, but tolerated the same dose (10 gm.) intravenously without any reaction. He died a few weeks after the last series of injections. Case 17 received 3 complete "courses" of nucleotid (10 gm. intramuscularly every day for 7 to 10 days and an extra dose intravenously on alternate days on 3 separate occasions) without any conclusive improvement in the granulocytopenic or clinical condition. This patient also died.

A summary of our experience with nucleotid is as follows: Two acute cases died before more than 1 or 2 injections had been administered; 3 chronic continuous cases were uninfluenced either hematologically or clinically by adequate dosage of the material and all are dead of the disease.

Summary and Conclusions.—1. The significant data of 18 cases of agranulocytic angina (pernicious leukopenia) are reported with 9 necropsies. All but 4 are dead (78 per cent mortality). Of these 4 only 2 can be considered cured.

2. The most promising treatment, aside from blood transfusion, seems to be pentose nucleotid (Jackson), although our experience with this substance has not been favorable. It seems more definitely to be useless in chronic cases of the disease.

3. Necropsy study has shown in more than half the cases thus examined by us a plentiful supply in the leukopoietic centers of the progenitors of the blood leukocytes. This virtual hyperplasia is in marked contrast to the profound peripheral leukopenia characteristic of the disease, and strengthens the previous suggestion⁴ of an hypothesis of primary "maturation arrest," rather than primary "aplasia" to account for the hematologic phenomena of the disease.

4. Agranulocytic angina (pernicious leukopenia) seems to be a disease entity, although it is so closely simulated by certain other conditions that its nosologic status may remain debatable until a potent specific therapy is available, or some other pathognomonic feature is discovered.

NOTE.—For permission to report Cases 3, 6 and 15 we are indebted to Dr. T. Grier Miller and for Case 5 to Dr. Edward Rose. Our patient, Case 16, entered the Mount Sinai Hospital a few days before his death and we are indebted to Dr. S. L. Israel for his report of the clinical data covering this period and to Dr. R. N. Meranze, Director of Laboratories of the Mount Sinai Hospital of Philadelphia, for his excellent report of necropsy findings. We have had contact with 2 additional cases of this disease (both fatal) which we are not at liberty to include in this report. One of these also received adequate nucleotid therapy without ensuing benefit.

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DIAPHRAGMATIC HERNIA ASSOCIATED WITH SECONDARY ANEMIA.

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ALTHOUGH diaphragmatic hernia was formerly considered a rare condition,¹ the present popularity of Roentgen ray in gastrointestinal examination has resulted in this type of hernia being commonly demonstrated.^{2,3,4,5} With more and more cases of diaphragmatic hernia diagnosed, it has been generally noted that some of the cases have an associated anemia.⁶ So far as known, the English literature has not offered a collection of cases on this association, and it is therefore the purpose of this paper to present brief summaries on 22 previously published cases in the English literature and additional summaries on 6 unpublished cases.

Case Reports. CASE 1.—A man,⁷ aged 43 years, complained that for a year he had suffered from exhaustion which occurred upon arising and was only relieved by prolonged resting. For several years he had had a sour stomach and, during the last few months, some epigastric pain which was relieved by soda. The appetite was fair and there had been only a few pounds loss of weight. The Roentgen ray showed a gastric ulcer of considerable size located on the lesser curvature of the pars media and a hernia of the cardiac portion of the stomach through the esophageal opening of the diaphragm. The stool on the meat-free diet was free from occult blood during our examination. There had never been a history of tarry stools, and to his knowledge occult blood had never been demonstrated in the movements. The blood showed a secondary anemia: hemoglobin, 42 per cent; red blood cells, 3,670,000; color index, 0.58; white blood cells, 7,850; neutrophils, 74 per cent; lymphocytes, 22 per cent; eosinophils, 4 per cent.

The degree of secondary anemia was unusual in our experience, particu-

larly in cases of gastric or duodenal ulcer, which have no history suggestive of bleeding and present no occult blood at the time of their examination. It is therefore interesting to note that all symptoms and Roentgen ray findings disappeared and the blood count became normal and remained so upon prescribing a modified Sippy ulcer régime.

CASE 2.—A woman,⁸ aged 50 years, complained of frequent bilious attacks and vomiting for 15 years. Roentgen plates showed a large, diaphragmatic hernia containing one-half of the stomach. The blood showed: hemoglobin, 60 per cent; red blood cells, 4,100,000; color index, 0.73.

CASE 3.—A woman,⁸ aged 51 years, was troubled with gas after eating and for the past several months had weakness, dizziness and palpitation. Stools showed occult blood. A gastrointestinal Roentgen ray study demonstrated a diaphragmatic hernia. The blood showed: hemoglobin, 55 per cent; red blood cells, 3,800,000. The patient was operated upon and no structural cause for the anemia was found, either at the site of the herniation or other sites along the intestinal tract. The hernia was not reduced and occult blood and anemia persisted.

CASE 4.—A woman,⁸ aged 73 years, had tarry stools 4 years ago, and occult blood during the last 2 months. There was no indigestion, although the gastrointestinal Roentgen ray study demonstrated a diaphragmatic hernia. The blood showed: hemoglobin, 45 per cent; red blood cells, 2,500,000.

CASE 5.—A woman,⁹ aged 59 years, was in an automobile accident 9 years ago following which she experienced epigastric pain. Recently she had vomited coffee ground material. Blood examination showed: hemoglobin, 75 per cent; red blood cells, 4,720,000. She was operated upon, and a diaphragmatic hernia containing a greater portion of the stomach was corrected. She was relieved of her trouble. Harrington believes this case was congenital in origin, as the automobile accident was trifling and there were vague digestive upsets prior to it. Bleeding was supposedly due to a demonstrable erosion of the stomach mucosa at the site of the hernia.

CASE 6.—A woman,⁹ aged 60 years, had indigestion for 35 to 40 years. Blood was noted in the gastric contents. Blood study showed: hemoglobin, 68 per cent; red blood cells, 3,650,000. The Roentgen rays had demonstrated an extensive diaphragmatic hernia. The patient was operated upon with relief of symptoms.

CASE 7.—A woman,⁹ aged 54 years, had suffered a marked kyphosis since 5 years of age due to a fall. Since that time she had always had heartburn and indigestion. Four years ago she had experienced a severe pain in the left side of the thorax. A physician had treated her for some time for anemia, and had noted blood in the stools. Blood examination showed: hemoglobin, 46 per cent; red blood cells, 3,700,000. Operation was performed and a thinning of the gastric wall at the site of angulation through the hernia was noted. The hernia was satisfactorily reduced and 4 months later the blood showed: hemoglobin, 95 per cent; red blood cells, 5,400,000.

CASE 8.—A boy,⁹ aged 12 years, complained of vomiting for 9 years and hematemesis during the past year. Blood study showed: hemoglobin, 70 per cent; red blood cells, 4,500,000. Operation was performed disclosing all of the stomach and part of the transverse colon through the diaphragmatic hernia. Because of the bleeding, the patient had been treated for gastric ulcer.

CASE 9.—A woman,⁹ aged 49 years, had epigastric pain and vomiting since childhood. Recently she had vomited blood several times. The Roentgen plates showed an ulcer at the point of angulation of the stomach through the hernia. At operation no ulcer was noted, although there was definite thinning of the gastric wall at this point.

CASE 10.—A woman,⁹ aged 59 years, had attacks of epigastric pain associated with dyspnea for 12 years. Examination of the blood showed: hemoglobin, 58 per cent; red blood cells, 3,700,000. At operation the cardiac portion of the stomach was found through the hernia and a gastric ulcer high on the stomach near the cardia. It was thought that this was a congenital hernia with a true inflammatory ulcer.

CASE 11.—A man,⁹ aged 35 years, suffered a severe fall 8 years ago and for the last 6 years had stomach trouble. His hemoglobin was 70 per cent and the red blood cells 4,520,000. Blood was present in the vomitus. Operation disclosed a greater part of the stomach through a hernia with shallow ulceration at the point of angulation.

CASE 12.—A young boy⁹ had stomach trouble due to a diaphragmatic hernia. His hemoglobin was 20 per cent. There was no hematemesis or melena. Operation was decided upon and a phrenicotomy was done prior to an abdominal approach. With this measure only the gastric symptoms were relieved and the hemoglobin had risen to 68 per cent at the end of 3 months.

CASE 13.—A man,¹⁰ aged 55 years, had suffered from lower sternal pain after eating. The gastrointestinal Roentgen ray study showed one-third of the stomach in the hernia, and an ulcer in that portion just beneath the diaphragm. On medical treatment the pain disappeared, and at the end of 6 weeks Roentgen rays failed to demonstrate an ulcer crater. One year later the symptoms returned with occult blood and occasional vomiting of dark-colored material. The Roentgen plates demonstrated a recurrence of the ulcer. Operation was performed and the patient died of shock.

CASE 14.—A man,¹⁰ aged 58 years, had hematemesis in 1922. In 1927 he had pain in the lower left chest and in 1928 the stools showed occult blood with another attack of hematemesis. The hemoglobin dropped from 62 to 42 per cent. The Roentgen plates showed a diaphragmatic hernia with large gastric ulcer. The patient was operated upon, but died from the shock.

CASE 15.—A girl,¹¹ aged 19 years, was poorly developed, anemic, had dysmenorrhea and scattered chest pains. An operation was performed for a pelvic condition without relief. A second operation was performed some time later which showed a diaphragmatic hernia. This was corrected and the patient was relieved of all her trouble.

CASE 16.—A boy,¹² aged 7 years, had frequent vomiting spells. Blood study showed: hemoglobin, 65 per cent; red blood cells, 3,400,000. Operation was performed for correction of a diaphragmatic hernia and the patient was relieved.

CASE 17.—A woman,¹³ aged 45 years, suffered from abdominal colic for 4 to 5 years which was produced by food and required morphin for relief. Blood study showed: hemoglobin, 64 per cent; red blood cells, 3,920,000. At operation three-fourths of the stomach was removed from the diaphragmatic hernial opening, and the patient was relieved.

CASE 18.—A man,¹⁴ aged 42 years, had a left side pain 16 years ago while wrestling, and since then had recurring attacks of abdominal distress. No blood was noted in the gastric contents which showed normal acid, nor was there blood in the stools. "The blood gave a picture of secondary anemia of moderate grade." Fluoroscopic examination showed most of the stomach in a diaphragmatic pouch. A recent communication from one of the authors states that this patient has progressed on medical treatment, and "his blood picture is better than 10 years ago; he now has only a moderate grade of secondary anemia."

CASE 19.—A woman,¹⁵ aged 65 years, suffered from epigastric distress for 10 years with sour eructations and infrequent vomiting. The blood count showed: hemoglobin, 45 per cent; red blood cells, 2,000,000. Roentgen rays demonstrated a diaphragmatic hernia.

CASE 20.—A woman,¹⁶ aged 52 years, had epigastric distress after meals for 1½ years which was relieved by belching. The stools showed occult blood, but the gastric contents showed none and there was a hyperacidity. "She had a moderate secondary anemia." The gastrointestinal Roentgen ray series showed a duodenal ulcer and herniation of the stomach through the diaphragm. The hernia was reduced and a posterior gastroenterostomy was performed, with relief of symptoms. One and a half years later the hernia returned, but the patient remained asymptomatic and there was no recurrence of the anemia.

CASE 21.—A woman,¹⁶ aged 51 years, had weakness of such severity during the past year as to force her to give up work. There was no digestive trouble with the exception of constipation. The blood study showed: hemoglobin, 50 per cent; red blood cells, 3,800,000. The stools repeatedly showed occult blood. She was operated upon and the stomach was examined for bleeding, but no source was discovered; neither was any malignancy noted. A diaphragmatic hernia was not touched and the anemia persisted so that 10 months later it was of such severity as to make the patient a chronic invalid. No other cause of this anemia has been ascertained.

CASE 22.—A boy,¹⁷ aged 16 years, had vomited after excessive eating since the age of 18 months. The blood showed "a decided diminution in red corpuscles, and normal number of white cells with hemoglobin 70 per cent." An operation disclosed the pylorus, duodenum, some omentum and liver herniated into the right chest cavity.

CASE 23.—A boy,¹⁸ aged 19 years, had epigastric pains after meals for 8 months. This was relieved by vomiting, but with no hematemesis. "On admission to Guy's Hospital the patient was very thin and anemic." The Roentgen rays showed a left diaphragmatic hernia which was operatively corrected. The surface of the stomach was inflamed and bruised near the pylorus from friction against the front and inner edge of the hernial opening.

CASE 24.—A boy,¹⁹ aged 2½ years, had weakness and pallor since birth. His blood showed: hemoglobin, 20 per cent; red blood cells, 2,800,000. His condition was diagnosed as anemia of unknown origin, and it was found that well to iron. Later he died of bronchopneumonia, and it was found that almost the entire stomach and portion of the duodenum was through the right diaphragm. No mention was made of ulceration or bleeding points.

CASE 25.—A woman,²⁰ aged 45 years, had noted a burning epigastric pain for a few months, and which was relieved by alkalies. Four years ago she had similar trouble at which time bleeding into the intestinal tract was noted. Blood examination showed: hemoglobin, 35 per cent; red blood cells, 2,760,000. Gastrointestinal Roentgen ray series showed a right diaphragmatic hernia. The patient was transfused and then operated upon with correction of the hernia. No cause of bleeding was noted. One month later the hemoglobin was 67 per cent; however, a recent communication states that the hernia has returned and with it a recurrence of the anemia.

CASE 26.—A woman,²⁰ aged 41 years, had been pale for several years, and 3 years ago was successfully operated upon for hemorrhoids. One year ago the hemoglobin was 18 per cent, and a blood transfusion was given. Now she presented pain in the left upper quadrant which radiated to the shoulder blades, and the blood showed a hemoglobin of 40 per cent with red blood cells 2,500,000. The stool was negative for occult blood, and a normal amount of gastric acid free from blood was noted. Operation disclosed the cardiac portion of the stomach in a left diaphragmatic hernia, and no mention was made of a bleeding point. The patient expired from a post-operative bronchopneumonia.

CASE 27.—A woman,²¹ aged 34 years, states that 1 year before she was very anemic, and now suffered from palpitation and dyspnea. For some

time she had gas and bloating after heavy meals. The blood showed: hemoglobin, 30 per cent; red blood cells, 3,580,000. The stools were positive for occult blood. An operation disclosed the stomach, a large loop of the transverse colon, and the first part of the small intestine in a right-sided diaphragmatic hernia. The hernia was satisfactorily reduced. The hemoglobin, 5 months later, was 65 per cent; 8 months later it was 72 per cent, with red blood cells, 4,000,000. This hernia was considered congenital and no bleeding point was made out.

CASE 28.—A woman,²² aged 64 years, presented a diaphragmatic hernia under the Roentgen ray. Several members of her family had a similar condition. As long as remembered she had been anemic. A recent blood count gave hemoglobin 55 per cent and red blood cells 3,750,000. Other data were lacking.

Discussion. These cases have been selected because they illustrate cases of diaphragmatic hernia in which there was definite blood loss, an anemia, or both.

The literature is considered inaccurate in determining the dependence of anemia on the hernia, as many cases are presented from the Roentgen ray viewpoint, as well as from a medical or surgical angle, and the blood picture has not been closely considered. Those cases of traumatic diaphragmatic hernia followed by immediate gastrointestinal bleeding have not been included in the series. These are a problem for the traumatic surgeon.

In analyzing the above series 17 are females and 11 are males, making the anemia more common in the former. Age is a factor, as 19 cases occurred after the age of 40 years. Twenty-five cases are thought to be congenital; only 3 have a possible traumatic cause. This difference is probably due, as stated above, to the fact that traumatic cases with immediate bleeding have not been included.

As usual, in cases of diaphragmatic hernia, the gastrointestinal symptoms may be of such a mild nature that the patient does not ask for medical aid for many years. Twelve cases had symptoms of indigestion running from 6 to 35 and 40 years; 1 middle-aged patient had trouble since "childhood." Nine cases has trouble for a period of months only, and 7 cases did not mention any gastrointestinal complaints. When symptoms are noted, however, they are suggestive of any type of abdominal upset. Fourteen of the cases had demonstrable loss of blood; so that coupled with their complaints, the impression of a bleeding ulcer is given rather than of a diaphragmatic hernia.

The rôle of ulceration in causing anemia is most important. This ulceration may be a true peptic one, independent of the hernia as demonstrated in 5 cases, or a definite abnormality in the gastric mucosa as shown in 5 cases. In the true peptic ulcer group Case 13 illustrates a temporary relief of all trouble on a medical regimen directed toward the ulcer. With the reappearance of the ulcer crater 1 year later, and a return of symptoms and bleeding, the ulcer and not the hernia was responsible for his anemia. Case 1

also demonstrates that the ulcer is a most important factor, as ulcer treatment resulted in the blood count returning to normal. Case 20 is similar in that operative treatment was given for both the ulcer and the diaphragmatic hernia with relief. This relief continued even after the recurrence of the hernia. Case 10 responded to operative treatment directed toward both the ulcer and the hernia. It is felt that in Case 14 the large gastric ulcer was responsible for the anemia. These cases, therefore, indicate that the hernia was a coincidental finding, with anemia produced by bleeding from true peptic ulcers. The fact that more peptic ulcers are not noted with diaphragmatic hernia also indicates that the herniation does not necessarily predispose to peptic ulcers.

In contrast to these cases are those with an abnormal mucosa at the site of herniation. Cases 5, 9, 11 and 23 showed such definite changes when their mucosa was inspected at operation. Case 7 must also be included in this group, and is of special importance because a follow-up blood count was made after the operation. Before operation her count was hemoglobin 46 per cent with red blood cells 3,700,000 and 4 months later was red blood cells 5,400,000.

The most interesting and perplexing cases of all are those with anemia which present no apparent anatomic cause for bleeding, and whose only unusual finding is the diaphragmatic hernia. In Cases 6, 15, 16, 17, 22 and 26 it is merely stated that an operation for hernia correction was performed, and no other gastrointestinal lesion was noted. We are led to believe that these operations were successful and that the anemia was corrected, although no definite follow-up reports were given. Case 27 is one in which operation disclosed no bleeding point; yet, after correction of the hernia we are given definite figures to indicate that the hemoglobin rose from 30 to 72 per cent in 8 months. The hernia here probably caused the anemia. In Cases 3 and 21 no bleeding points were noted, the hernia was not reduced and the anemia persisted with no other apparent cause. Case 18, although not presenting apparent blood loss, did show an improvement on "medical treatment" in his secondary anemia. This anemia, however, still persists to a lessened degree. Case 25 indicates a decided relationship between the hernia and the anemia. An operation to correct the hernia was followed by a rise of hemoglobin from 35 to 67 per cent in 1 month; however, the hernia returned and so did the anemia.

Case 12 stands alone in that only a phrenicotomy was done and nothing else; yet the hemoglobin rose from 20 to 68 per cent in 3 months. We might suppose that paralysis of the diaphragm relieved considerable vascular tension in the gastric wall with no further oozing of blood.

Cases 2, 4, 8, 19, 24 and 28 merely report a diaphragmatic hernia with a secondary anemia present.

In all these cases there is only one type of anemia apparent, and

that is the secondary type. This is determined on the low color index, the lack of nervous changes, the absence of glossitis and the presence of free gastric acid when a test was made for it.

No work has been done to show just how the hernia can produce an anemia, though two possibilities present themselves. One is that there is some obscure change in the gastric mucosa which may result in a deficiency productive of an anemia. In this series only 4 cases have a definite mention that a bleeding point was not found when looked for at operation. All of these cases had a history or demonstration of blood loss. None of them had a histologic examination of the stomach mucosa, and none showed an achlorhydria when tested for. This series, therefore, does not contain sufficient evidence to assume there is a gastric deficiency productive of an anemia. The second possibility is that of blood oozing from the gastric mucosa due to venous congestion, caused by compression of the stomach by the diaphragmatic muscles; that is, the cause of the anemia would be a mechanical one. In those cases where there is no demonstrable bleeding point, one must always eliminate other sources of blood loss.

The treatment of these cases with anemia depends upon a most careful study to exclude frank ulceration. If this condition can be demonstrated the usual medical ulcer regimen such as diet and alkalies with secondary anemia therapy should be instituted. However, if this treatment does not relieve distressing symptoms or the anemia and there is no other demonstrable cause for the anemia an operation should be done. The ulcer should be considered as of the greatest importance in these circumstances. In cases in which only the hernia is present and no other cause for the anemia is apparent a try at the medical ulcer treatment is again worth while. If the symptoms of anemia are sufficiently distressing and the medical treatment is a failure, surgery should be instituted.

Summary. 1. Twenty-two previously published and 6 previously unpublished cases of diaphragmatic hernia with an associated anemia are briefly summarized.

2. Of these cases presented, sex, age, cause, duration of symptoms and character of symptoms are briefly discussed.

3. Of the 28 cases, the diaphragmatic hernia was a primary factor in producing anemia in 8 cases, true peptic ulcer was a complicating factor in 5 others. Insufficient data, postoperative death and the possibility of an anemia of unknown origin eliminated 3 other cases. The other 12 cases allow only the supposition that the anemia was caused by the hernia.

4. The anemia is secondary in type, being caused, it is thought, by venous oozing due to a compression of the stomach by the diaphragmatic muscles.

5. Treatment consists of the medical ulcer regimen, including diet and alkalization, plus secondary anemia treatment. If this fails,

and if the anemia is severe, surgical correction of the lesions present is worthy of consideration.

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PARENTERAL LIVER EXTRACT THERAPY IN THE TREATMENT OF PELLAGRA.

A PRELIMINARY REPORT.

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THERE is still a wide difference of opinion as to the exact etiology of pellagra although it is generally believed that a deficient diet plays the major rôle in its causation. Based on this belief the usual treatment consists, essentially, of a diet rich in vitamin G or Goldberger's P.P. factor. Underhill¹ thinks that a lack of vitamin G is not the sole factor, and that too much reliance should not be placed on this agent in the prophylaxis and treatment of the disease. He quotes Turner's view that vitamin G therapy has made a poor showing and that this is probably an argument against its specificity.

Mellanby² suggests a double deficiency as the cause, a lack of vitamin G being responsible for the skin lesions, and a lack of vitamin A being responsible for the cord lesions. Guthrie,³ in a review of 336 cases, found a high incidence of achlorhydria and, like other observers suggests that there is possibly a relationship between pellagra and pernicious anemia. Cohn, Minot, *et al.*, from their study of pernicious anemia, were doubtful that the antipellagra vitamin was responsible for the effectiveness of liver in the treatment of that disease, but stated that further investigation was being done by them.

Wheeler and Sebrell⁵ have tested 35 foodstuffs for their efficiency in the prophylaxis and treatment of pellagra, and one of these, liver, was found to be rich in vitamin G. Goldberger and Sebrell⁶ found that liver extract, when fed to dogs on a basic diet, prevented and relieved black tongue and suggested that it might be a valuable temporary expedient in the treatment of pellagra. Boggs and Padgett⁷ in a review of a series of 102 cases also stressed the value of *liver* in the diet (not liver extract).

At Parkland Hospital our most difficult problem in the treatment of pellagra has been the patient's coöperation in the dietary régime. Loss of appetite is a marked feature of the disease, and most patients refuse to eat sufficient food. Many of them refuse to take such foods as milk, fresh meats and green vegetables. Therein lies the probable reason for many observers reporting poor results in the treatment of the disease, thus discounting the efficiency of vitamin G therapy.

In view of this difficulty and, also, to try out the clinical value of liver extract in the treatment of pellagra, we decided to use the parenteral method of administration. Our treatment consisted of rest in bed and a general house diet without any additional vitamin G containing foods. Liver extract No. 343 was given in daily doses of 2 cc. intramuscularly without variation. The usual site of injection was the deltoid or gluteal region. Practically no inconvenience was experienced from the injections. No other medication of any kind was used.

Twenty-two cases were treated in this manner, 20 in the hospital and 2 outside. The results have been spectacular. The earliest change in the symptoms was a rapid return of the appetite. In every case, in from 3 to 7 days, the appetite became either normal or in many cases ravenous. In our experience this never occurred in the usual dietary treatment when the disease was active. Cowgill⁸ has shown that dogs have an abrupt loss of appetite in from 3 to 5 days, when fed a diet free from undifferentiated vitamin B and that when the vitamin is restored the appetite returns in a few days.

The general clinical improvement was rapid in all cases. No deaths occurred in the series, which is also remarkable. The gastro-

intestinal, skin, mental and nervous symptoms improved much more rapidly and completely than with the dietary treatment in previous cases. The average time of hospitalization was much shorter than previously.

There was a moderate amount of anemia in all cases. In a few cases in which reticulocyte counts were made the response was not marked (the highest was 4.7 per cent). Achlorhydria was present in 81 per cent of the cases.

A brief summary of some of the most severe cases will illustrate the efficiency of the treatment.

Case Abstracts. CASE 10.—Mrs H. B., white, aged 59 years, a farmer's wife, was admitted to the hospital on August 5, 1932, with intense burning of the forearms and lower legs, sore mouth and loss of appetite. There was no history of a previous attack; however, she stated that for the past year she had had frequent attacks of colic. Constipation had been present for many years. She was greatly depressed and unable to give a connected history.

Examination revealed: a white woman much older in appearance than the age would indicate. There was moderate emaciation. The skin was in fair condition and apparently normal except on the arms and legs. A very inflamed symmetrically distributed dermatitis of the bullous type covered both forearms from the wrists to and including the elbows, and both lower legs from the ankles to a short distance below the knees. The mucous membrane of the mouth was very inflamed. The tongue was thick and beefy looking, and along its margins there were several necrotic ulcers. The temperature was 104° F., the pulse 120, the red cell count 4,190,000, hemoglobin 80 per cent. The gastric contents showed no free hydrochloric acid.

Liver extract was started the day of admission. Five days later the appetite had greatly improved and the temperature was declining. The sore mouth had improved to such an extent that eating was not painful. No local treatment was used on the blistered areas. On the 7th day the patient was alert mentally, and requested that she be given more food. By the 13th day the temperature was normal and the dermatitis had disappeared leaving smooth, healed, pinkish-looking areas. On the 19th day the patient left the hospital free of all clinical evidence of pellagra.

CASE 3.—Mrs. P., white, aged 52 years, a farmer's wife, was admitted to the surgical service on May 10, 1932, because of profuse bleeding from the rectum. No surgical condition was found and she was transferred to the medical service. For the past 20 years she had suffered from indigestion following each meal. Most of the time she had passed large quantities of gas. She had had 7 children and had had many spontaneous abortions. There had been intermittent pains in the epigastrium for 10 years, and for 6 years there had been an intermittent bleeding from the bowels. The latter had occurred frequently during the past year, and with every bowel movement for the past month. She had gradually lost weight for several years, amounting to a total of 50 pounds. For 3 years shortness of breath had been very distressing, at times requiring her to stop and rest before she could speak. Spells of vomiting were frequent and always followed a meal in which some article of food had disagreed with her. Her appetite had been poor for many years, and she had confined her diet largely to cereals because of the epigastric pain. There had been alternate constipation and diarrhea, but no history of any previous dermatitis.

Examination: the skin was very dry and rough over the entire body, and in many small areas there was marked desquamation. In each flank

there was an area 18 by 12 centimeters in which the skin was very rough and pigmented, giving it a dirty yellowish color. Above each heel across the tendo Achillis the skin was in large, rough, pigmented folds. The hands were rough, and especially across the knuckles, the skin was pigmented. The reflexes were moderately exaggerated, with slight general spasticity. The mental responses were slow. The basal metabolic rate was -3 . Achlorhydria was present.

Liver extract was begun May 17, 1932 and on June 14, 1932 the patient was discharged clinically well. One month after leaving the hospital her weight had increased 40 pounds. There was no evidence of pellagra, all symptoms having completely disappeared. At this time this woman was doing her housework and also helping in the fields.

A report from this patient on January 24, 1933, indicates that the mental responses and body weight are normal. The skin on the forearms is slightly rough. The gastrointestinal tract is showing some disturbance, evidenced by occasional indefinite abdominal pains. However, she has drifted back to her old habit of restricting her diet. In all probability there will be a recurrence of the pellagra syndrome this summer.

CASE 13.—Mrs. H., white, aged 42 years, a farmer's wife, was admitted to the hospital August 5, 1932. Three years previously while 7 months pregnant, she had an acute illness which was diagnosed influenza, but she delivered normally at term. Since that time she had gradually lost weight and strength. For the past 6 months she had been practically helpless due to weakness and stiffness. And for the past 2 months she had been confined to the bed.

Examination revealed a marked general spasticity with greatly increased reflexes. Walking was slow and unsteady. The face was expressionless. The tongue could not be protruded beyond the teeth and swallowing was difficult, the food regurgitating through the nose. The arms were strongly flexed at the elbows and the hands held across the chest with the thumbs down into the palms. The arms could be only partially extended by force, and this was painful. The speech was very slow and deliberate and almost unintelligible. A pregnancy of 4 months complicated the picture. The abdomen was greatly distended with gas. The skin was dry, and in each flank there was a large area in which the skin was rough and pigmented. The face, neck, and lower legs up to the knees presented a yellowish tanned appearance as if sun burned. The general picture was that of a Parkinsonian syndrome and pellagra.

The patient had daily injections of 2 cc. of liver extract, beginning August 12, 1932, and continuing until October 12, 1932, except for 1 week when they were discontinued inadvertently. Improvement was noticed after the first week and was continuous until the patient was discharged October 12, 1932. After 1 month of treatment the muscular spasticity had improved sufficiently for her to fold surgical dressings. At the present time, 1 month after leaving the hospital, the improvement is continuing, although no liver extract has been given except orally since her discharge. The facial expression is now nearly normal. No difficulty is experienced on swallowing. There is no rigidity of the neck muscles. The left arm shows some spasticity and is held in flexion, but can be straightened without pain. The appetite is normal. The gait is steady. The pregnancy is developing in an apparently normal manner. The tanned appearance of the skin has disappeared, except on the face. This patient is now doing her housework including the cooking for a family of 5.

Baker, Bradley and Longcope,³ in a study of the effect of liver therapy on the neurological manifestations of pernicious anemia, found that improvement was noted in 59.9 per cent of the signs and

symptoms in 8 patients after more than 10 months' treatment. Continuous treatment of neurological manifestations of pellagra with liver extract may likewise cause more improvement than formerly as is evidenced in the above case.

CASE 6.—Viola W., mulatto, laundress, aged 28 years, married, was admitted to the hospital on July 7, 1932, complaining of extreme weakness and abdominal pain. For 3 months she had been feeling weak, lost her appetite, and her abdomen began to distend with gas. Her hands and feet began to get black 3 weeks before admission. One week later her mouth became sore, and sores appeared on her hands.

Examination: the most noticeable sign was a very marked emaciation, so extreme that she could not stand without holding to the bed. There was a slight general spasticity with the elbows and knees flexed. The knee jerks were greatly exaggerated. There were fine tremors of the fingers and tongue. Mentally the patient was slow. Depression was so marked that she did not notice what was going on about her. The abdomen was distended and extremely tender throughout. The mucous membrane of the mouth was fiery red. The tongue was thick, red, and had several small necrotic ulcerations. The skin across the backs of the hands, tops of the feet and lower abdomen was a sooty black. Across the knuckles of each hand was a thick black crust with multiple small bleeding points. Around the vagina there was an inflamed area about 2 inches wide which showed less pigmentation than the other areas. The temperature was 101° F., and the pulse rapid. The red cell count was 4,250,000, and hemoglobin 80 per cent, white cells 7600.

Liver extract was begun July 12, 1932, and 1 week later the crusts on the backs of the hands were easily peeled off with tissue forceps. The underlying skin was smooth and free from bleeding points. The temperature varied from 101° to 102° for the first week. For the next 2 weeks it was irregular and rose at times to 101°, after which it remained normal. The appetite was normal after 1 week's treatment. General improvement began early and continued rapidly. The patient was discharged from the hospital August 27, 1932, free from pellagra symptoms and much improved in weight. We have not been able to follow this patient since her discharge.

With our former cases in this hospital the death rate has varied, but normally, with the dietary form of treatment, we would have expected probably 4 or 5 deaths in a series of 22 cases. In the present series no deaths have occurred. In all probability Cases 6, 10 and 13 of this series would have died if the treatment had been dietary alone.

Strong evidence has recently been developed which seems to prove that a close relationship exists between pellagra and pernicious anemia. Strauss and Castle¹⁰ have shown that the "extrinsic" factor concerned in the production of pernicious anemia is definitely related to vitamin B₁₂, if not vitamin B₂ itself.

Conclusions. 1. Twenty-two unselected cases of pellagra were treated with liver extract intramuscularly without a death and with rapid marked clinical improvement. We believe that severe cases in either young or old people, which often prove fatal in a short time, can be treated successfully with liver extract.

2. In patients with severe mental depression or marked gastro-

intestinal disturbances who refuse to eat, this method of treatment will give quicker results than dietary treatment.

3. It is simple and much easier to carry out than dietary treatment.

4. A combination of liver extract and the usual dietary treatment would probably give better results than either alone.

5. The time of hospitalization is greatly reduced.

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NOTE.—Reference 6 is the only reference we have found in the literature on the use of liver extract in the treatment of pellagra. Also we have found nothing which dealt with the parenteral use of liver extract in the prophylaxis or treatment.

In reference 7, Boggs and Padgett stress the value of *liver* in the dietary treatment.

REVIEWS.

PUBLICATIONS OF THE COMMITTEE ON THE COSTS OF MEDICAL CARE. No. 28, *Medical Care for the American People*. The Final Report of The Committee on the Costs of Medical Care, Adopted, October 31, 1932. Pp. 213. Chicago: The University of Chicago Press, 1932. Price, \$1.50.

THIS final report of the Committee on the Costs of Medical Care has already been so widely discussed that in a general way its contents are doubtless known to the medical profession—and well they should be, too, as the topic is undoubtedly the most important that will come to this generation of medical men for its decision. And decided it must be, if not by the profession, then by others for them. The time, ability and energy put into amassing and correlating the material for the 28 reports of which this is the summary will hardly ever be equalled for this purpose again; so that whatever our reactions to the conclusions presented, we much recognize our debt to the small group of men who initiated the study and to the foundations that made the study possible.

And how can this report best serve the problem—which can be crudely stated as: how to provide adequate medical at feasible costs. The interpretation of “adequate” is the greatest obstacle in the way of accepting the majority report and the Reviewer agrees with its critics that it is difficult to visualize a highly organized group system of medical care that will preserve the necessary individual relation of physician to patient and avoid the mechanical inefficiency of governmental agencies and the evils of political control on the one hand or the unnecessary exploitation of unscrupulous private combines on the other. No reason is apparent why medicine should take this plunge rather than any other of the basic activities of our national life and certainly the experiences of the various national health insurance schemes in Europe should not lead us to copy them. The minority report, on the other hand, though it recommends the careful trial of new methods, is in effect so unreservedly a bid for a *statu quo* which has proved increasingly impractical that it offers but little constructive guidance to a solution of the problem, especially of its “feasible cost” element. We cannot but regret, then, that the Committee did not content itself with a presentation of facts and, resisting the pressure that of course would be exerted for a statement of recommendations, allow the situation to continue to evolve along the slow and painful lines of trial and error, and the gradual formation of national opinion. The facts presented do not give adequate basis for action and we do not believe that Social Studies have advanced to the point “that Social Evolution may be guided wisely.” The times do not yet seem ripe to have any revolutionary change in this fundamental item of civic service forced into operation and the premature effort which this report may precipitate will necessarily produce more heat than energy.

There is one detail about the high cost of medical care that we have not seen emphasized—namely, the unnecessary costly procedures in handling simple cases, which after all constitute well over 90 per cent of the cases seen by physicians. Granted the practitioner's recollection of needed “thorough study of the case” in teaching students, his fear that the half educated family or friends of the patient will otherwise think he is being neglected, the estimate of what the traffic will stand and many similar psychological reasons, nevertheless the evil of unnecessary expense to the patient looms ominously. If the sick of the nation could be given adequate care without frills, we suspect that by this step alone the high cost of medical care would be materially lowered. The half billion dollars wasted annually on quacks and nostrums is another item worth remedying. E. K.

PUBLICATIONS OF THE COMMITTEE ON THE COSTS OF MEDICAL CARE. No. 22. *The Fundamentals of Good Medical Care*. An Outline of the Fundamentals of Good Medical Care and An Estimate of the Service Required to Supply the Medical Needs of the United States. By ROGER I. LEE, M.D., and LEWIS WEBSTER JONES, PH.D., Assisted by BARBARA JONES. Pp. 302; numerous tables. Chicago: The University of Chicago Press, 1933. Price, \$2.50.

ALTHOUGH it is far beyond our space limitations to review all the publications of the Committee on Medical Care, we must make an exception for this item on account of its wide sphere of usefulness. Perusal of the first 90 pages by the "intelligent layman" would go far toward reducing prevalent misconceptions about the medical profession, while the remaining section on the medical needs of the people would be equally illuminating to physicians. We agree, too, that "the provision of good medical care is largely a question of organization and costs," a problem to be solved in part at least by conscious redirection of medical activities. "The actual provision of adequate medical care must therefore wait upon a practical solution of the problems of economic organization, in which the questions of cost and the means of payment are paramount. It involves also the solution of difficult problems of technical organization, which will assure not only quantitative sufficiency, but above all the quality of service which can be realized only by the maintenance of the traditionally high standards of the medical professions." E. K.

HOW TO BUDGET HEALTH. Guilds for Doctors and Patients. By EVANS CLARK, Director, Twentieth Century Fund, Inc. Pp. 328; 12 illustrations. New York: Harper & Bros., 1933. Price, \$4.00.

THIS work, published by the Twentieth Century Fund, whose President, Edward A. Filene, was one of those most active in the formation of the Costs on Medical Care, may be looked on as a sequel to the publications of that Committee. Focussing on the principles of group practice and group payment recommended in the majority of the Committee's report, this book is a layman's advocacy of a "medical guild plan." A frankly *ex parte* presentation, it suffers from the defects of unbalanced partiality as well as from a lack of appreciation of the basic importance of the individual relation of doctor to patient. As a clear presentation of a definite plan from one side of the doctor-patient combination, it is a useful adjunct to the Committee's literature. E. K.

ACROMEGALY. By F. R. B. ATKINSON, M.D., C.M., EDIN. UNIV. With a Foreword by SIR ARTHUR KERTH. Pp. 260; 3 illustrations. London: John Bale, Sons and Danielsson, Ltd., 1932. Price, 21s.

THE author furnishes a digest of the clinical appearance, pathological anatomy, symptoms and causes, the course of the disease, the various types, pathogeny, diagnosis and treatment of this affection.

The literature has been thoroughly sifted and from 1319 cases elaborate tables present the results of removal of the pituitary gland, the analysis of postmortem examinations, description of the eye conditions, and clinical symptoms and a full bibliography covering 64 pages and 1600 references. While no original work is presented (except for three illustrations of one typical case), the work constitutes a most valuable compend of the subject.

The publishers have done their full part with splendid paper and print. Perhaps the section on laboratory technique (page 63) should be expanded in such a way as to cover sporotrichum, blastomyces, monilia, and so forth, in which case it would deserve a more independent position—perhaps among the fundamental considerations.

These technical errors do not in any way detract from the value of the book as a whole, which has been most useful in bringing together the widely scattered mycologic information on one hand, with the clinical features which have already become much more widely known. The book finds no counterpart in the English language, and if for no other reason merits place in mycologic literature. Jacobson has rendered a distinct service in bringing together a notable accumulation of mycological information.

F. W.

THE PSYCHOLOGIC EFFECT OF MENSTRUATION. By MARY CHADWICK. Pp. 70. New York and Washington: Nervous and Mental Disease Publishing Company, 1932. Price, \$2.00.

THE odd and abnormal doings at the menstrual period are here given free Freudian interpretation. Upon primitive woman, it is intimated that the seemingly cruel restrictions imposed, may have been necessitated by her own aberrancy.

N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Asthma, Hay Fever and Related Disorders. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Attending Physician, Cook County Hospital, Chicago. Pp. 124; 8 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$1.50.

A Standard Classified Nomenclature of Disease. Compiled by The National Conference on Nomenclature of Disease. Edited by H. B. LOGIE, M.D., C.M., Executive Secretary. Pp. 701. New York: The Commonwealth Fund, 1933. Price, \$3.50.

Irrtümer der Medizin. Neue Gedanken über das Blut- und Nierenproblem. By KURT BERGEL. Pp. 92; 18 illustrations. Leipzig: Bong & Co., 1933. Price, 3 M.

The Committee on the Costs of Medical Care. No. 22. *The Fundamentals of Good Medical Care.* An Outline of the Fundamentals of Good Medical Care and an Estimate of the Service Required to Supply the Medical Needs of the United States. By ROGER I. LEE, M.D., and LEWIS WEBSTER JONES, Ph.D., Assisted by BARBARA JONES. Pp. 302; numerous tables. Chicago: The University of Chicago Press, 1933. Price, \$2.50. *Abstract No. C 2. The Purchase of Medical Care Through Fixed Periodic Payments.* By PIERCE WILLIAMS. Pp. 18. Washington, D. C.: The Committee on the Costs of Medical Care, 1932. (No price given.)

Nurses. Production, Education, Distribution, and Pay. Report by the Committee on the Grading of Nursing Schools, presenting a few of the outstanding findings from the 2-year study of nursing economics which it carried on in order to secure a fast basis for grading schools of nursing. Pp. 36; 11 illustrations. New York: Committee on the Grading of Nursing Schools, 1930.

- How to Budget Health. Guilds for Doctors and Patients.* By EVANS CLARK, Director, Twentieth Century Fund, Inc. Pp. 328; 12 illustrations. New York: Harper & Bros., 1933. Price, \$4.00. (For Review see page 575 of this Journal.)
- Chemical Wave Transmission in Nerve.* Based on the Liversidge Lecture Delivered at Cambridge on May 13, 1932. By A. V. HILL, F.R.S., Foulerton Research Professor of the Royal Society; Honorary Fellow of King's College, Cambridge. Pp. 74; 13 illustrations. New York: The Macmillan Company, 1932. Price, \$1.25.
- Office Surgery.* By FENWICK BECKMAN, Visiting Surgeon, Bellevue Hospital; Visiting Surgeon, Hospital for the Ruptured and Crippled, etc. (Everyday Practice Series, Edited by HARLOW BROOKS, M.D.) Pp. 402; 94 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.
- Chronic Arthritis and Fibrositis.* By BERNARD LANGDON WYATT, M.D., F.A.C.P., Director, The Wyatt Clinic, etc. Pp. 201; 17 illustrations. Baltimore, William Wood & Co., 1933. Price, \$3.50.
- Food in Health and Disease.* By KATHERINE MITCHELL THOMA, B.A., Director of Dietetics, Michael Reese Hospital, Chicago. Pp. 370. Philadelphia: F. A. Davis Company, 1933. Price, \$2.75.
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- Crimes and Criminals.* By WILLIAM A. WHITE, A.M., M.D., Sc.D. Pp. 276. New York: Farrar & Rinehart, 1933. Price, \$2.50.
- Physical Chemistry of Living Tissues and Life Processes.* By R. BEUTNER, M.D., Ph.D., Professor of Pharmacology, School of Medicine, University of Louisville. Pp. 337; 79 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$5.00.

NEW EDITIONS.

- Calcium Metabolism and Calcium Therapy.* By ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College, etc. With a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., Late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Pp. 262. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$2.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Effect of Dietary Calcium and Phosphorus on Toxicity of Lead in the Rat; Rationale of Phosphate Therapy.—Several years ago Aub and his associates presented a scientific therapeutic régime in lead poisoning based upon the fact that the metabolism of calcium and lead apparently has a definite parallelism. When there is a negative calcium balance, calcium, and lead if it is present in the body, is deposited in bone. With a positive calcium balance there is an increased elimination of calcium and lead. The solubility of lead phosphate is analogous to calcium phosphate, so that the lead is deposited in the bone in a manner similar to that of calcium. The addition of calcium salt to diets in general results in an increased storage of lime salts in the bone trabeculae. It was also thought by Aub that the deposition of lead in the bone might be almost instantaneous. This, however, has not been proven and seems to be unlikely. In this new study, in so much as improved calcification of bone following the administration of calcium salts does not take place unless there is adequate phosphorus in the diet, the handling of the patient with lead poisoning has been undertaken on the basis that a certain definite proportion of phosphorus must be included with the calcium. Furthermore, on theoretic grounds alone, it is held that the aim of the treatment of lead poisoning is to deposit or excrete lead in an innocuous form, the phosphate and an abundance of foods containing phosphorus should be given. SHELLING (*Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 248) tested the hypothesis that the introduction of large amounts of calcium without phosphorus merely diverts the available phosphorus to rid the body of excess calcium as a phosphate with consequent interference with the formation of lead phosphate. Thirty-two rats were used, divided into 8 groups of 4 each and were given calcium carbonate, magnesium carbonate, lead carbonate and Na_2HPO_4 in various preparations, together with viosterol. In some instances it was found that the animals receiving vitamin D died sooner than those which did not receive the vitamin, suggesting that the vitamin diverted calcium phosphate into the bones and allowed the lead, uncombined with phosphate, to circulate freely with the body fluids. In the Na_2HPO_4 group, when the phosphate was adequate for both deposition and excretion of both calcium and lead, the animals

did well. Some of the animals were fed the stock diet of lead carbonate until toxic and then were put upon calcium in one group or phosphate in another group. Those receiving the phosphate did well, while calcium-fed animals did poorly. When the phosphate was withdrawn and lead was substituted, the animals did very poorly. The sudden intake of calcium to excess liberated the stored lead causing toxic manifestations. These results indicate that it is essential that a sufficient amount of phosphate be given in the diets of those people suffering from lead poisoning. Aub gives milk, which contains considerable calcium and abundance of phosphorus, but others, not realizing the importance of the phosphorus factor, give large doses of calcium salts other than the phosphate. The phosphate in conjunction with the calcium is important not only in depositing lead in the bones during the acute attacks but also in attempting subsequently the deleading of the individual. This can be done by giving a diet low in calcium and high in phosphorus so that cations taken from the bone are eliminated as insoluble phosphates.

SURGERY

UNDER THE CHARGE OF

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Antiseptics for Skin Sterilization.—During the past 10 years a number of organic mercurial preparations have been offered the profession for use in wound and skin sterilization. In each instance various claims have been made for the superior antiseptic properties of the new substance. In 1925 TINKER and SUTTON (*Ann. Surg.*, 1925, 82, 640) studied the efficiency and inefficiency of certain skin antiseptics. They found that if the skin was smeared with resistant nonpathogenic bacteria, a soap and water scrub for 2 minutes gave a skin free from bacteria in 30 per cent of cases. Careful ward preparation followed by an ether swab on the operating table gave a skin free from bacteria in 75 per cent of cases, and reduced the colonies in the remainder to a maximum of 3. They found that the selective action of antiseptics was so important that it seemed unwise to depend upon any single antiseptic for skin preparation. Their investigations lead them to the conclusions that iodine preparations and picric acid were too inefficient under ordinary circumstances to be depended upon. Five per cent acriflavin proved to be the most efficient antiseptic which the authors investigated. A 5 per cent solution of mercurochrome in 50 per cent alcohol was approximately as potent as 5 per cent iodine. One year later (*J. Am. Med. Assn.*, 1926, 87, 1347) the same authors stated that "iodine, trinitrophenol, Harrington's solution, mercurochrome and potassium mercuric iodide will not kill most of the resistant and some of the less resistant, pathogenic bacteria under conditions of perfect contact, and

are still less efficient if penetration is required." They believed that the anilin dyes warranted further investigation and probably wider use. Since these papers the number which have been published on the subject is too lengthy to mention. Many are open to serious question from the standpoint of the technique involved while others have failed to use a sufficiently wide variety of organisms to warrant the claims made in the papers. The frequent sources of error very probably account for the many contradictory notes which have recently been published. The antiseptic properties of the solution may vary with the pH as was shown by HILLER and STAMLER (*J. Urol.*, 1929, 22, 699), DAVIS (*AM. J. MED. SCI.*, 1921, 161, 251) and TODD (*Lancet*, 1925, 2, 1017). BROWNING, COHEN, ELLINGWORTH and GULBRANSEN (*Proc. Roy. Soc. London*, 1930, 105, 99) and MORGENROTH (*Deutsch med. Wchnschr.*, 1919, 45, 505) have shown that the presence of serum and proteins may affect the antiseptic properties of the solution. It is interesting that this fact is not considered by most of the pharmaceutical houses in advancing claims for the antiseptics which they are manufacturing. It should be emphasized that culture experiments on different species may be misleading.

BIRKHAUG (*J. Am. Med. Assn.*, 1930, 95, 917) found the bacteriocidal efficiency of mereurochrome was less than that of hexyl-resorcinol, mercuric chlorid and iodine, but higher than that of phenol. In determining the phenol coefficient of mereurochrome for different organisms the author found these to be as follows: *S. aureus*, 1.7; *S. hemolyticus*, 3; *B. coli*, 2; *B. anthracis*, 4.6; *B. subtilis*, 3.7. SIMMONS (*J. Am. Med. Assn.*, 1928, 91, 704; *J. Infec. Dis.*, 1926, 39, 273; *Surg., Gynec. and Obst.*, 1933, 56, 55) found that a 2 per cent solution of mereurochrome failed to kill the *S. aureus* in 2 minutes or the *S. scarlatinae* in 5 minutes. It did, however, kill the *S. pyogenes* in 2.5 minutes. Simmons found that all mereurochrome solutions which he tried failed to kill the spores of *B. anthracis* in 3 hours, which was accomplished by tincture of iodine in 1 hour. The papers of TINKER and SUTTON (*J. Am. Med. Assn.*, 1926, 87, 1347), REDDISH and DRAKE (*J. Am. Med. Assn.*, 1928, 91, 712), RAIZISS, SEVERAC and MOETSCH (*J. Am. Med. Assn.*, 1920, 94, 1199), SIMMONS (*J. Am. Med. Assn.*, 1928, 91, 704; *Surg., Gynec. and Obst.*, 1933, 56, 55), SCOTT and HILL (*J. Urol.*, 1925, 14, 135) and SCOTT, HILL and ELLIS (*J. Am. Med. Assn.*, 1929, 92, 111) report contradictory results on the bacteriostatic and bacteriocidal properties of the various antiseptics used on the skin. A recent report by GERSHENFELD and MILLER (*J. Am. Pharm. Assn.*, 1932, 21, 894) presents convincing evidence that the bacteriocidal properties of certain of the proprietary organic mercurial preparations are probably in large part due to the acetone and alcohol present in the preparations used for skin sterilization in surgical practice. Although REDDISH and DRAKE (*J. Am. Med. Assn.*, 1928, 91, 712) reported results from which they concluded that a 2 per cent acetone-alcohol solution of mereurochrome was as efficacious as iodine, the recent studies of SIMMONS (*Surg., Gynec. and Obst.*, 1933, 56, 55) fail to confirm this, and Simmons infers that Reddish has obtained similar data since his publication. The claims that the new organic mercurial antiseptics penetrate into the deeper tissues of the skin and subcutaneous tissues have not been confirmed by more recent investigations (VON OETTINGEN, *J. Am. Med. Assn.* 1932, 99, 127;

BISKIND, *Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 37). Tincture of iodine is probably the most commonly used skin antiseptic. Its chief disadvantage is that it frequently irritates the skin. An aqueous iodine solution has been proposed by KARNS (*J. Am. Pharm. Assn.*, 1932, 21, 779) which is less irritating. BISKIND (*Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 37) found that Karn's solution penetrated the skin more rapidly than did alcoholic solutions of iodine, and GERSHENFELD and MILLER (*J. Am. Pharm. Assn.*, 1932, 21, 894) found the antiseptic qualities of the two solutions similar. It is evident that we do not as yet have an ideal skin antiseptic. It should always be borne in mind that painting the skin with an antiseptic solution does not render the part bacteriologically sterile. All that one can hope to attain is relative freedom from harmful bacteria. Cleanliness is of primary importance.

THERAPEUTICS

UNDER THE CHARGE OF

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Renal Diathermy in Renal Hypertension.—Although employment of diathermy in kidney disease goes back a number of years, there is as yet no uniformity of opinion either as to its effects or its therapeutic value. In order to obtain specific data as to its effects RAUSCH (*Deutsch. med. Wchnschr.*, 1932, 58, 1440) conducted a considerable series of accurately controlled observations upon patients whom he divided into three groups as follows: Group I was made up of those with hypertensive nephrosclerosis in its early stages in which the hypertension was definitely labile; Group II, the same type of patient in the more advanced stage where the hypertension was more or less fixed; Group III comprised patients with chronic nephritis with its secondary hypertension. In the patients in the first group systematic diathermy carried out over periods of several weeks brought about a significant and more or less lasting reduction in blood pressure although this was never brought down to a normal level, the average fall lying between 40 and 60 mm. of mercury. These effects were observed to last for weeks or even months after the cessation of treatment. Striking as they were, the relief of subjective symptoms was even more pronounced in this group of patients. After a few treatments the tendency to vertigo, headache, the sense of pressure within the head, general hyperexcitability and sleeplessness all showed either marked diminution or disappeared practically completely. Similar though far less pronounced effects were produced in the second group. In this group, however, the reduction of blood pressure was insignificant and such benefits as

resulted from the treatment we limited chiefly to some diminution in the subjective symptoms. In the third group no benefit was observed except by way of relief of symptoms especially of the persistent headache. The author discusses the probable mechanisms involved in these effects and points out that they rest chiefly upon an improvement in renal and extrarenal blood flow, both directly and probably indirectly. His technique consisted in placing an electrode of 60 sq. cm. area over each kidney posteriorly and a single lead electrode of 200 sq. cm. over the upper abdomen where it was held by a sandbag. This method of application appeared to place the kidneys most directly within the field of current. The current employed depended upon the patient's sensitiveness to heat and usually lay between 1 to 2 amperes, and the duration of treatment between 45 and 60 minutes. The author feels that the method is of definite help in the treatment of these 3 forms of renal hypertension and that his observations define closely the nature and degree of benefits to be expected.

PEDIATRICS

UNDER THE CHARGE OF

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The Therapeutics of the Intravenous Drip.—HYMAN and HIRSHFELD (*J. Am. Med. Assn.*, 1933, 100, 305) state that in hemorrhage or dehydration, the intravenous drip will directly restore the fluid volume. In the treatment of shock, the drip acts apparently as a corrective for the underlying abnormality in the distribution of the blood. The drip fulfills a twofold purpose in the management of infections. It functions both as a supportive measure and as the ideal route for the administration of specific therapeutic measures. To the surgeon this method possesses value both as a prophylactic against unpleasant postoperative complications and as a therapeutic measure once these untoward events have been established. It may act as a supportive to maintain the patient through a prolonged or shock-producing procedure, and it tends to prevent shock, postoperative thyrotoxicosis, and certain of the common postoperative intestinal disturbances, such as nausea and vomiting, postoperative distention of the stomach, and anuria. By means of the drip the normal level of the blood pressure may be maintained during spinal anesthesia and during exposure of the central nervous system, as during these conditions there may be marked and often alarming fall in blood pressure. The method is of value to the internist in the treatment of toxemias and metabolic abnormalities such as diabetic coma, uremia, cholemia and the intestinal intoxications of infancy and childhood. The dextrose solution also supplies energy, particularly when the enteral routes of administration are not available. There is also some reason to think that the method may be of value in conditions associated with osmotic and colloidal changes in the central nervous system such as occur in poliomyelitis and in encephalitis. In the matter

of the solution used the author's experience was limited to three fluids: physiologic solution of sodium chlorid, dextrose in physiologic solution of sodium chlorid, and blood. They found no occasion for the use of acacia. Dextrose, 5 or 10 per cent, in physiologic salt solution introduced at the rate of 2 or 3 cc. per minute will supply 3000 to 4000 cc. of fluid from 150 to 400 gm. of dextrose yielding from 600 to 1600 calories and adequate salt. Where there is edema or any fear of salt retention, the dextrose may be given in distilled water. If glycosuria occurs, appropriate amounts of insulin may be added directly to the dextrose solution. Other drugs may be administered through the drip such as soluble hypnotics and morphin, epinephrin, digitalis and the like. It also furnishes a convenient avenue for the administration of blood.

The Chemical Action of Sodium Citrate as a Cause of Certain Transfusion Reactions.—DODD and BRYAN (*Am. J. Dis. Child.*, 1933, 45, 32) point out that dogs with certain chemical abnormalities of the blood are very susceptible to sodium citrate. They show severe and sometimes fatal reactions following the injection of the amounts of citrate ordinarily used as an anticoagulant in blood transfusions. It is probable that children with similar changes in the blood would have the same increased susceptibility to sodium citrate. Although studies on guanidin were not begun when it was first surmised that citrated transfusions were sometimes harmful, poor results have been seen in conditions that the authors now believe to be associated with increased guanidin in the blood. Guanidin is known to have toxic effect other than the production of nervous hyperexcitability and gastrointestinal irritation. Among these are disturbances in carbohydrate metabolism, brought about by interference with the normal metabolism of lactic acid. This condition as well as the nervous symptoms are relieved by calcium. The authors have found that the increase in guanidin level that is associated with severe diarrhea is persistent until normal fluid equilibrium has been reestablished. Since calcium medication does not decrease the guanidin but merely combats its effects, it seems obvious that any reduction of active calcium by the introduction of citrate might increase the toxic action of the guanidin even in cases in which no marked reaction is precipitated. This may account for the earlier impression that children with gastrointestinal indigestion were sometimes made worse by transfusion of citrate. It seems to make no difference in the reaction whether the sodium citrate reaches the blood stream through gastrointestinal absorption or by direct injection. This suggests that the oral administration of sodium citrate to combat acidosis may be dangerous for children with gastrointestinal indigestion. The ill effects of citrated transfusions of blood in infants with diarrhea may be prevented by the injection of calcium gluconate. As the disadvantages of the citrate method can be so readily overcome by the previous injections of calcium gluconate, the disadvantages are outweighed by the obvious advantages of this method in children. While the intravenous injection of calcium salts is not always free from danger, it has been found that the slow injection of from 3 to 10 cc. of a 10 per cent solution of calcium gluconate is a safe procedure.

Whooping Cough: A Study in Immunization.—SAUER (*J. Am. Med. Assn.*, 1933, 100, 239) used from 7 to 8 cc. of a relatively fresh pertussis vaccine made from recently isolated, hemolytic strains. These he injected hypodermically in divided weekly doses and seems to have immunized an appreciable number of young susceptible children. During the past 4 years about 300 non-immune children have been injected without any untoward effect. The local reaction is transient. The leukocyte count on the day of the last injection in 60 per cent of the cases ranged from 12,000 to 15,000 per c.mm., with the percentage of small lymphocytes often increased. There have been 8 certain cohabitational or household exposures, and a total of 127 probable or transient or accidental exposures, without any child contracting whooping cough. The 8 cases of definite contact seem to lead to the conclusion that this amount of vaccine will protect, if the interval between injection and exposure is not less than 3 months. Of the 109 children in Group A in 82 instances there were intimate exposure without any child contracting the disease. Among the 94 children of Group B there were 29 such exposures without the development of a case. In Group C consisting of 88 children there were 16 contacts without a case developing. This study is reported at the end of 4 years because the evidence seems sufficiently reassuring to encourage the testing of this method of immunization by others. Use of commercial strains are warned against as long cultivation in the laboratory lead to loss of virulence.

DERMATOLOGY AND SYPHILIS

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Clinical Observations on Tabetic Arthropathies (Charcot Joints).—KEY (*Am. J. Syphilis*, 1932, 16, 429) analyzes the records of 69 patients with various expressions of the Charcot arthropathy. He points out that it occurs in from 4 to 10 per cent of tabetics and 25 per cent of cases of syringomyelia. It is distinctly a disease of late adult life, occurs more frequently in males, may involve multiple joints but mostly commonly affects the knee (39 cases), foot and ankle (29 cases), hip (15 cases), spine (5 cases); and joints of the upper extremities rarely (4 cases). In this series of cases only 3 had been precipitated by trauma. The onset may be very acute with apparent resolution of the joint with subsequent recurrence or more commonly the chronic phase supervenes. In all of the cases here reported there was either clinical or serologic evidence of neurosyphilis. One-third of the cases came solely for relief of the joint condition and were unaware of its

constitutional background. The most constant pathologic finding in the entire group was abnormalities of the pupils, only 2 patients having normal pupillary findings. Ninety per cent showed loss of deep reflexes. Among 60 cases subjected to serologic study, the Wassermann was positive in 19 and negative in 41 and in 30 patients with spinal fluid findings, the spinal Wassermann was positive in 11 and negative in 19. While the author advocates aggressive active treatment of the underlying neurosyphilis, he does not believe that treatment will prevent the development of a Charcot joint or stay the progress of a joint already undergoing this type of destruction.

Syphilis and Thyroid Disease With Special Reference to Hyperthyroidism.—NETHERTON (*Am. J. Syph.*, 1932, 16, 479) gives an exhaustive review of the literature dealing with the association of syphilis and dysfunction of the thyroid gland and analyzes 62 cases from the records of the Cleveland Clinic to ascertain the proper management of such cases. The author cites cases in which syphilis produces a syndrome closely simulating hyperthyroidism, but the basal metabolic rate was within the range of normal. The author concludes that: (1) Antisyphilitic treatment should not replace surgical intervention in cases of active hyperthyroidism in syphilitic individuals, as operation followed by antisyphilitic therapy will prevent the cardiac damage which may result from the unnecessary delay. (2) Syphilis does not interfere with the convalescence of these cases. (3) Pre-operative treatment is advisable but should not be too vigorous. (4) Patients having neurosyphilis associated with hyperthyroidism are poor surgical risks, especially if there is mental deterioration.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Primary Diphtheria of Vulva in Childhood.—Having reviewed the Russian and German literature on the subject, SMORODINZEFF (*Zentralbl. f. Gynäk.*, 1932, 56, 2118) concludes that primary diphtheria of the vagina and vulva in childhood is a rather unusual disease. After reporting 3 cases of his own he sums up the factors which should aid in making the diagnosis. The most important symptom is painful urination and it is usually the reason for consulting the physician. There is general weakness and nervous restlessness, but the body temperature is normal or only slightly elevated. The external genitalia are markedly edematous, much more so than is seen in gonorrheal vulvovaginitis. The inguinal glands are enlarged and hard. There is a slight, blood-tinged,

mucous discharge in contrast to the profuse purulent discharge seen in gonorrhea. On the vulvar mucous membrane can be found a gray or grayish green membrane which is strongly adherent to the underlying tissues, which bleed when an attempt is made to remove the membrane. In gonorrheal infection the mucous membrane is usually very hyperemic, but in diphtheria there is a characteristic cyanotic appearance and, as a rule, several deep erosions are present. For positive diagnosis, of course, resort must be had to bacteriologic study. The treatment of this condition embraces the usual rules for the treatment of diphtheria. Antitoxin should be given in adequate dosage remembering that intramuscular injection is about six times as efficient as subcutaneous administration, while in very ill cases intravenous injection may be necessary.

Surgical Accidents to Ureter.—Accidents to the ureter during the course of a pelvic operation probably occur with greater frequency than usually reported but, according to BEACH (*J. Urol.*, 1932, 28, 35), most of them can be forestalled. The risk is greater in vaginal hysterectomy and occurs not so often in ligating the broad ligaments as in seizing obscure "bleeders" at the vaginal vault. The Wertheim operation is particularly treacherous and the originator of this operation is alleged to have had 44 ureteral fistulae (6 per cent) following his own technique. Precise anatomic knowledge, including morbid deviations and preliminary ureteral catheterization for complicated cases, will prevent disaster. The ureter is most often injured in hysterectomy especially for cancer and frequently for the removal of intraligamentous tumors. The usual sequel is a ureterovaginal fistula. Complete ureteral section disrupts the neuromuscular mechanism of this organ and usually dooms the kidney. The pace of kidney dissolution is determined somewhat by the remedial measure adopted. The best reparative measure is the implantation of the proximal ureter into the bladder when possible. Even ideal ureteral anastomosis often culminates in segmental atony or stricture with superimposed infection. Nephrectomy should be a last resort, since the other procedures transfer the load gradually to the opposite side, and it should never be done at the time of the accidental injury.

OPHTHALMOLOGY

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Amaurosis in the Preëclamptic State.—According to MAYER (*Zentralbl. f. Gynäk.*, 1931, 55, 3490), the occurrence of amaurosis as the initial symptom of an eclampsia does not increase the severity of the prognosis for the life of the mother, and conservative treatment can be

employed, if desirable in the interests of the child, if the general condition and renal function of the mother warrant. In a certain percentage of cases the amaurosis is thought to be a functional disturbance without an anatomic basis. No fundus changes are present and the vision soon returns to normal. In other cases, retinitis, hemorrhages or retinal detachments are present. In such cases immediate induction of labor is necessary to save sight. As a rule, amaurosis is only a precursor of true eclampsia, and convulsions will soon follow. In an occasional case, however, under conservative management, vision returns to normal in a few days and the pregnancy continues to term without further complications. Treatment by means of lumbar puncture to reduce the intracranial pressure, and by venesection to lower the blood pressure and for its detoxicating effect, seems to have little influence on the amaurosis. The same holds true for intradural injections of normal pregnant serum. The luminal, Stroganoff, and hunger-diet measures for the control of the convulsions seem not to affect materially the course of the amaurosis. To summarize, latent eclampsia with amaurosis as the initial symptom should be handled in the same way as eclampsia without amaurosis. Conservative treatment is usually of little value from the standpoint of the child because of the frequency of intrauterine death, but, from the standpoint of the life of the mother, carries no greater risk than in eclampsia without amaurosis. For the conservation of the future vision of the mother, delay should be considered only if the fundus is normal.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Vidian Neuralgia.—VAIL (*Ann. Otol., Rhinol. and Laryngol.*, 1932, 41, 837) says that "vidian neuralgia" is a pain of neuralgic character in the nose, face, eye, head, neck and shoulder, occurring in severe attacks. These cannot be caused by any external stimulation, are not relieved by opiates and are not associated with any subjective loss of sensation. The attacks are most typically unilateral, are often nocturnal and may or may not be associated with subjective symptoms of a nasal sinusitis. After enumerating the various subjective and objective findings of Sluder's sphenopalatine ganglion neuralgia, the author refers to his previously reported case (*Arch. Surg.*, 1929, 18, 1247) of sphenoiditis which presented "not only the posterior symptoms hitherto assigned to irritation of the vidian nerve, but also the anterior symptoms which Sluder felt were due to irritation of Meckel's ganglion. Believing Sluder to be in error by attempting to differentiate between sphenopalatine ganglion neuralgia and vidian neuralgia, and that the symptoms in the condition under discussion are due to an irritation or inflammation of the vidian nerve and not to any conditions affecting directly the sphenopalatine ganglion, the author quotes anatomic facts to refute Sluder's experiments and "to show that it is impossible to

stimulate the vidian nerve in the sphenomaxillary fossa without involving the sphenopalatine ganglion." Of his 31 personal cases, 28 were in females. He concludes that treatment should be directed towards the disease in the sphenoidal sinus.

Adenoids and Upper Respiratory Disease (Common Cold) in Adults.—Purposing to ascertain any existant relationship between the presence of the pharyngeal tonsil (adenoids) and the frequency, severity and type of attack of the common cold in adults, GAFAFER (*Ann. Otol., Rhinol. and Laryngol.*, 1932, 41, 517) conducted a series of observations on 252 men and 65 women. Investigations extended over the 35 weeks from October, 1929, to June, 1930. Of the entire group of 317 persons, 235 showed adenoids. As portrayed in the author's tabulations, the presence or absence of adenoids did not seem to make any significant difference in respect of frequency, severity, or type of attack of upper respiratory disease (common cold).

RADIOLOGY

UNDER THE CHARGE OF
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Röntgenologic Manifestations of Giant-cell Tumor.—In a series of 86 proved cases of giant-cell tumor, 2 roentgenologic types of growth have been encountered with approximately equal frequency by KIRKLIN and MOORE (*Am. J. Roent. and Rad. Therap.*, 1932, 28, 145). The first variety has been accurately described by many observers. It is a central tumor, situated most often in the end of a long bone, and it exhibits trabeculae and expands the cortex but does not break through it. Other tumors of bone which may be confounded with this type of giant-cell tumor are enchondromas and cysts of bone. In the second type of giant-cell tumor trabeculation is conspicuously absent. The roentgenograms give evidence of homogeneous lysis of the affected area; the cortex is not only expanded but is dissolved wholly or in part, and the tumor projects into the soft tissues. In many cases the irregularly destroyed cortex has the appearance of a thin layer of melting ice. This variety of giant-cell tumor might be mistaken for primary sarcoma or a massive metastatic growth. Giant-cell tumor is not necessarily confined to the end of a long bone; exceptionally it may occur elsewhere in the shaft. Besides the long bones, the bones of the face, the vertebrae, the ribs and the tarsal bones are subject to the disease. In this series outstanding differences from other series reported were not observed in respect to age and sex of the patients or duration of the disease.

Roentgenologic Evidence of Fetal Death.—From roentgenologic studies of 176 cases of pregnancy including 16 cases in which the fetus was dead, SCHMITZER, HODGES and WHITACRE (*Am. J. Roent. and Rad. Therap.*, 1932, 28, 349) draw the following conclusions: Roentgenographic demonstration of overlapping of the skull bones of a fetus *in utero* is fairly reliable evidence that the fetus is dead, provided the patient is not in labor and that care has been taken to exclude pseudo-overlapping due to the overlying images of sutures and fontanelles. Absence of overlapping means little. Conclusive evidence is lacking as to the exact relationship between the datum of fetal death and the development of the sign but all agree that some time must elapse. A faint fetal shadow may mask overlapping; hydrocephalus may prevent its development. Spinal angulation and thoracic collapse appear to be of doubtful value as criteria of fetal death. It is dangerous to diagnose decalcification in every instance of a faint or blurred fetal shadow, because early in pregnancy the appearance may be due to a failure to calcify rather than a loss of calcium previously present, and, even in well-calcified skeletons, excessive amniotic fluid, respiratory movement and many technical factors can produce the same appearance. Furthermore, quantitative information is lacking as to the calcium content of the human fetus, either macerated or normal, and some embryologists and clinicians insist that no decalcification occurs in maceration. Anthropometric data published by Scammon and Calkins allow a reasonably accurate opinion as to the age of a fetus if its occipitofrontal diameter is known. Even with very coarse roentgenographic measurements of this diameter, Roentgen estimates of fetal age have agreed surprisingly well with the actual age (as estimated from menstrual or delivery dates) in a considerable number of cases. Disproportion between ages thus calculated and the supposed duration of gestation constitutes a valuable criterion of fetal death and accurate fetometry by stereoroentgenographic methods ought to improve the validity of the diagnosis. Absence of any or all of the criteria does not exclude the possibility that a fetus is dead because they all depend upon the degree of maceration. It seems worth while, therefore, to point out that the roentgenographic diagnosis of movement of a fetal part occurring during the Roentgen examination constitutes conclusive evidence of fetal life.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Psychiatry in the Children's Institution.—MARKEY (*Am. J. Orthopsychiat.*, 1932, 2, 25) discusses the relationship of the psychiatrist to the children in an orphanage. In the opinion of the assistant superin-

tendent of the institution, a man who has been intensively psycho-analyzed, the psychiatrist may influence the general mental hygiene normally carried on in the institution, but his main service has been to treat directly children whose resistances are great and complex, whose behavior tends to be antisocial and whose personalities appear to be cracking under the strain of life. The psychiatrist's contacts have tended to resolve conflicts, to realign mental powers, to develop for such children a personal ally. The fairly well integrated children are enabled to find better values in life and discontent has been softened; thereby preventing unacceptable reactions. The author believes the psychiatrist has not been as helpful with antisocial as with shut-in children, perhaps because the former pass through all of the administrative levels first. The director of the after-care service believes the psychiatrist has been of great help in the development of wholesome attitudes on the part of the children toward their postgraduate life and its problems, that he has helped her to understand their problems better and to handle them more successfully. She adds that the friendly relationships established by the psychiatrist with children before their graduation makes it a simple matter to continue the contact, through intensive correspondence, even in instances where the children have gone to distant cities. The psychiatrist believes that he has become an integral part of the medical and social organization of the institution, but finds that his functions are limited because they overlap and might tend to repeat the professional angle of the administrative function. This, therefore, makes him less important and a less absolute support than the physician is in his field. He has, in psychiatric fashion, also avoided the use of absolute insistence on carrying out his recommendations and has tended right along to avoid encroaching on the administrative prerogative of decision. This has tended further to make him positive than the physician. An objective atmosphere has developed with a resultant lessening of dramatic reactions to acute problems and a probable decrease in the incidence of major problems. Treatment is now almost automatically based on cause; taboos and repressions play a minor part in discipline, and methods are now seen to be more valuable than results.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Systemic Effects of Histamin in Man.—An investigation upon the effects of histamin administered intravenously in the human subject has been recently carried out by WEISS, ROBB and ELLIS (*Arch. Int. Med.*, 1932, 49, 360). An average dose (0.001 mg.) was found to

produce flushing, an increase in the heart rate, electrocardiographic changes and a slight fall or rise in blood pressure. An increase in the pressure of the cerebrospinal fluid with a dilatation of the small cerebral vessels was also observed. The above changes occurred very rapidly and disappeared 2 or 3 minutes after the injection. Continuous intravenous administration of histamin in general produced similar effects, which lasted as long as the drug was given. Cardiovascular response depended upon the rate rather than the duration of the injection, the cardiac output being increased and the blood pressure remaining essentially unaltered. An elevation of the basal metabolic rate and a slight rise in the hemoglobin combining power were also noted. The respiratory mechanism was not appreciably affected. No subjective or objective changes were observed following the oral administration of histamin, even in massive doses. Attention is drawn to the similar effects of this drug and physical exercise. The absence of a fall in blood pressure and the failure of even toxic doses to produce symptoms of shock in the human subject would tend to discredit the rôle ascribed to histamin in the production of this condition.

Experimental Thromboangiitis Obliterans.—HORTON and DORSEY (*Arch. Path.*, 1932, 6, 910) in a series of experiments carried on over a period of 2½ years, report that they were able in many instances to produce vascular lesions in rabbits, similar to if not identical with the human lesion in thromboangiitis obliterans. This was accomplished by bacterial injection, or implantation of tissue known to be infested by similar organisms. The bacteria were cultured from 56 patients with thromboangiitis obliterans, and 10 patients with arteriosclerotic disease of the lower extremities. The organism most commonly present was a pleomorphic streptococcus. In addition green streptococci, staphylococci and Gram-negative bacilli were found. In a word, the authors were able to produce, in a fair number of instances, the described lesions with endothelial proliferation and thrombosis, by injection of pleomorphic streptococci, either intravenously or intramuscularly. The streptococci were those found in pure culture in bloodvessels of patients known to have thromboangiitis obliterans. Portions of vessels from patients with thromboangiitis obliterans were imbedded adjacent to femoral vessels with 24.1 per cent positive results. Results were 23.8 per cent positive in intramuscular injection, and 15.3 per cent positive in intravenous injection. Injection of organisms obtained from extracted teeth, tonsils and other foci of infection in thromboangiitis patients gave entirely negative results. The authors state that as far as they know, these are the first lesions of this type that have been produced in experimental animals and suggest that the disease is of infectious origin, possibly with the streptococcus as the etiologic agent.

The Induced Development of Nonacid-fast Forms of Bacillus Tuberculosis and Other Mycobacteria.—Since Koch, bacteriologists have been aware of the existence of nonacid-fast forms of the tubercle bacilli. Their place in the life cycle of the mycobacteria has not been generally accepted, since it has always been difficult to rule out contamination. MILLER (*J. Exp. Med.*, 1932, 56, 411) has been able, by adding a sterile extract of his "chromogenic H-37 strain of human tubercle

bacilli" to media on which certain acid-fast forms were growing, to wean these over to nonacid-fast forms. The strains were Saranac H-37, T. S., and 90, a bovine strain B-1, a smegma strain 74, and a Saranac strain of *Bacillus phlei*. Ten-day growths of the above mentioned strains were used in the experiments. One to 10 cc. of filtered extract was added to a fresh transplant of each of these growths. In some cases, second and third additions of extract were made before microscopic or macroscopic changes were noted. Transplants were made in 5 days, 2 weeks, 4 weeks, and 6 weeks. The organisms were finally grown on agar, and in many cases, smears of such growth were entirely nonacid-fast. In 4 of the strains, return to acid-fastness was induced by growth on Petroff's egg media. Peculiar morphologic changes are described. Control plates of the extract were always sterile. The fact that similar results were obtained in experiments carried on simultaneously in New York and Cleveland lessens the probability that contamination was responsible for the results obtained.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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6

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Public Health Aspects of Frozen Foods.—FELLERS (*Am. J. Pub. Health*, 1932, 22, 601) states that frozen food factories are clean and modern methods of sanitation are used in preparing the many perishables now packed. The quality of the raw product is high, and if the freezing is prompt and rapid and the storage kept at low, constant temperatures, little or no deterioration in quality, appearance or nutritive value occurs. Several types of very efficient mechanical equipment are available to carry out the freezing process. Fish, meats, poultry, eggs and oysters are especially well preserved by freezing because they retain more nearly their fresh appearance, flavor and character than fruits or vegetables. Most fruits are best when frozen with sugar and in this form retain their flavor very well. Vegetables are the most recent addition to the list of frozen foods. Though some varieties freeze very well, others do not. Both fruits and vegetables bleed freely on thawing. Spoilage occurs very quickly in vegetables after defrosting. More research is urgently required on the microbiology of frozen flesh foods and vegetables. Little change occurs in the chemical, enzymic or nutritive properties as a result of freezing. The changes are largely physical. Freezing greatly reduces the number of microorganisms present in foods and prevents their multiplication. Emphasis must be placed on the prompt utilization of frozen foods. Until more is known

about the subject, frozen products should be consumed while still frozen or within a very few hours after defrosting. The ready availability of a large variety of frozen foods at all seasons will serve to give variety to the human diet and should aid in decreasing nutritional deficiency diseases.

The Metamorphoses of Streptococci into Spore-bearing Rods and into Filtrable Forms.—EVANS (*U. S. Pub. Health Rep.*, 1932, 47, 1723) claim that a streptococcus, a filtrable form, and an aërobie spore-bearing rod are phases in the life cycle of an organism cultivated from cases of epidemic encephalitis and from the so-called herpetic and encephalitic viruses. The details of the transition from one form to the other are described in a few instances which exemplify metamorphoses that have been observed many times. The observations described in the present paper are discordant with the monomorphic theory, now discarded by most bacteriologists, but they are in agreement with the laws of general biology. As pointed out by the writer in an earlier paper (1929), from the point of view of general biology, complex life cycles with metamorphoses accompanied by changes in habitat and biologic behavior should be expected in bacteria, rather than monomorphism. Life cycles are a law of Nature; and with the descent in the scale of life, the cycles become more and more complex, and metamorphoses, with the concomitant changes in habitat and in biologic behavior, become more and more pronounced. Algæ, fungi and protozoa—the plant and animal groups stand next higher than the bacteria—exhibit marvelous life cycles. It is unreasonable to think that a law of Nature which becomes more and more complex with the descent in the scale of life would be suspended in its lowest known form.

Primitive or Filtrable Forms of Bacteria and Their Occurrence in Aseptic Milk.—BRUECKNER and SHERMAN (*J. Infec. Dis.*, 1932, 51, 1) have demonstrated that primitive forms of bacteria were present in the aseptically drawn milk of a majority of the healthy cows studied. The method used for the detection and quantitative estimation of these types of microorganisms was to make serial dilutions of the milk in dextrose beef infusion broth and to incubate the dilution cultures for 1 day at 37° C., and then at 30° C. for about 2 weeks. After incubation the broth cultures from the higher dilutions, which showed no growth of ordinary bacteria, were seeded on the surface of dextrose beef infusion agar. After incubation at 37° C. for 2 days the plates were examined microscopically for the presence of definite, minute colonies. Positive growths were verified by the finding of definite bacterial cells in stained preparations. The results reported in the present paper, as well as other work in the same laboratory, indicate that the primitive forms of bacteria may sometimes occur in numbers approximating a trillion (10^{12}) per gram of substance. The morphologic types observed were cocci and small rods. While the life cycle theory of previous investigators is a plausible and attractive explanation of the results obtained, the work reported here does not answer the question of whether these organisms are definite species or represent only a dissociative form or cycle-stage in the development of ordinary bacteria.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1933.

Criticism of Weighing by Single Deflections.—SAMUEL E. POND (Laboratory of Physiology, University of Pennsylvania). Analytical balances adapted for weighing by single deflections¹ have been critically examined for reproducibility of turning point over several months. One balance² has been employed regularly for rapid weighing of fresh tissues, routine quantitative analysis and for precision calibrations of weights in comparison with calibrations by other methods on more sensitive balances. Not only has time been saved but good accuracy has been maintained. Care had to be taken, however, to avoid changes observed in the reference point of the unloaded balance.

A source of varying error has been overcome by coördination of the beam lifting mechanism with the pan-arresting device, such as to prevent lateral displacement of the pointer. It was necessary in order to insure accuracy that the pointer-tip be adjusted to the top of one particular scale line, and this juxtaposition read with minimum of parallax, by means of lens and sight. Estimates were not made of distance, but always when coincidence was established. The major adjustment required that the right-pan stop be slightly clear from the pan at rest, at mean temperature. When and after this was done a high order of reproducibility of results was secured with temperature changes not exceeding 2° C. per hour outside the balance case. The same sensibility, at 7 seconds per half period, *i. e.*, ≈ 0.05 mg., with 100 gm. in each pan, has been maintained for several weeks. The reference point has varied less than 0.1 scale division from day to day. Calibrations of weights to 1×10^{-4} gm. have been completed in about 3 hours combining the method of substitution, *i. e.*, Borda's technique with single deflections, against 20 hours other things equal except that the method of oscillations was substituted. Similar materials, consisting of crucibles, have been conveniently weighed to $\approx 5 \times 10^{-6}$ gm., about 30 per hour, as against 8 per hour, comparing single deflections, checked three times, against —3:2 oscillations checked similarly.

Metabolism of Galactose in Diabetes Mellitus.—W. G. KARR, and T. V. LETONOFF (Laboratories of the Division of Metabolic Diseases, Philadelphia General Hospital). Much confusion has existed with regard to the metabolism of galactose. When it is given by mouth many investigators have found it disappearing from the blood very rapidly.

¹ Turner, R. R.: "Chemist-analyst," No. 16, 1916, p. 21; Brinton, H. M. P.: J. A. C. S., 1919, vol. 41, p. 1151.

² Troemner: No. 16.

Others have found a marked rise in total sugar and have formed the general conclusion that galactose is a poor glycogen former.

Tolerance studies in animals have more uniformly shown a decreased utilization. Cori and Cori¹ have also concluded, on the basis of feeding galactose to rats and analyzing their livers, that galactose does not form glycogen as readily as do glucose and fructose. Row and Schwartzman² repeated previous experiments done on normals and also did tolerance studies on diabetics. They concluded that galactose disappears from the blood as readily in diabetes as in normal individuals, and suggested that galactose might be more available to the diabetic than other carbohydrates.

Their experiments only included a 2-hour blood and urine study. It was thought that a study of galactose utilization in a diabetic over a longer period of time might throw additional light on its metabolism. A diabetic of long standing on the ward was chosen for the experiment. He was well controlled with insulin and diet, and at the time of experiment was on a diet of protein, 60; fat, 190; carbohydrate, 60; with 18 units of insulin in the morning and 12 at night.

For certain experiments insulin was withheld for 24 hours, and a study made of glucose and galactose tolerances. For the long time experiments 100 gm. of additional carbohydrate was given with his diet and insulin, divided in equal portions over the three meals. The increased glycosuria and glycemia were studied with the addition of galactose for one period, glucose and starch for similar comparative periods.

The comparative tolerance studies upon the patient without insulin for 24 hours showed the following results:

Galactose disappeared from the blood in 3 hours, and a certain portion was found in the urine. True glucose in the blood increased with the galactose feeding. The hyperglycemia from feeding equivalent amounts of glucose was much greater than the total sugar after galactose feeding. Sugars taken at 3.00 P.M., after a regular lunch, were of the same elevation, no matter what the carbohydrate fed, and continued so for the remainder of the day, and give similar fasting blood sugars the next morning. Respiratory quotient studies taken over this period showed that galactose was not burned in the body in any greater quantities than other ingested carbohydrates. There was a glycosuria after galactose feeding, but the glycosuria after glucose feeding was much greater.

On another day 50 gm. of galactose was given the patient with 18 units of insulin 15 minutes before the galactose feeding. The disappearance of the galactose from the blood stream with the previous dose of insulin was no greater than when insulin was not given. Insulin is not concerned with the removal of galactose from the blood.

Comparison of the long time experiments of feeding the carbohydrate three times a day, as indicated above, gave the following results:

On the galactose period the average urine glucose was 3.06 gm. daily. The average galactose excretion was 4.57 gm. During the glucose period the average daily glucose excretion was 9.42 gm. During the starch period the average daily glucose excretion was 7.01 gm. The average

¹ Cori, C. F., and Cori, G. T.: *J. Biol. Chem.*, 1926, 70, 557.

² Roe and Schwartzman: *J. Biol. Chem.*, 1932, 96, 717.

of 18 fasting blood sugars during the galactose period was 155 mg. per 100 cc.; during the glucose period 157 mg.; during the starch period 162 mg. The average of 11 fasting blood sugars on insulin and diet alone was 124 mg.

We may conclude from these experiments that the state of the diabetes, as measured by the fasting blood sugar, was the same in all three periods.

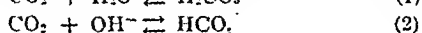
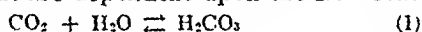
Glycosuria was slightly greater during the glucose period, as would be indicated by the previous tolerance experiments.

The following general conclusions may be drawn:

1. Galactose disappears very quickly from the blood in a patient with diabetes mellitus.
2. It is not burned, a small portion is excreted, probably little is changed directly to glucose, and it disappears so completely that it seems improbable that there is tissue storage. We are, therefore, able to suggest that galactose forms glycogen very readily in the diabetic.
3. Insulin does not aid in the removal of galactose from the blood stream.
4. Feeding of galactose for a period of a month does not suggest that it is valuable in diabetes, with the exception that the immediate glycosuria and hypoglycemia, after a meal, is somewhat decreased.

NOTE.—We are indebted to Smith, Kline and French, Philadelphia, for supplying the galactose without charge.

The Kinetics of CO₂ Reactions in Buffer Systems.—WILLIAM C. STADIE and HELEN O'BRIEN (From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia). The velocity of the reactions of all forms of CO₂ with the constituents of a buffer system are dependent upon the slow reactions



Toward the right, these equations express the *hydration* of CO₂, toward the left, the *dehydration* of carbonic acid. The velocity of the reaction (hydration or dehydration) is given by the equation

$$-\frac{d}{dt} {}^a\text{CO}_2 = k_{1a} {}^a\text{CO}_2 {}^a\text{H}_2\text{O} - k_{2a} \text{H}_2\text{CO}_3 + k_{3a} {}^a\text{CO}_2 {}^a\text{OH}^- - k_{4a} \text{HCO}_3^- \quad (3)$$

Two general cases arise.

I. The reactions occur in infinite buffer, *i.e.*, the pH is constant. Equation 3 may then be integrated and gives two equations (1) for hydration and (2) for dehydration which permit the calculation of the time necessary to reach any degree of equilibrium, *e.g.*, 90 per cent from the experimentally determined values of the constants k_1 , k_2 , k_3 , and k_4 .

II. The reactions occur in dilute buffer, *i.e.*, the pH is variable. Three cases arise.

1. The pH is < 8.5. Reaction 2 becomes negligible.

(a) The hydration of CO₂. The velocity is given by the equation

$$-\frac{d}{dt} {}^a\text{CO}_2 = \frac{d}{dt} {}^a\text{HCO}_3 = k_{1a} {}^a\text{CO}_2 {}^a\text{H}_2\text{O} - k_{2a} \text{H}_2\text{CO}_3 \quad (4)$$

This equation may then be integrated and the velocity constant k_1 determined experimentally from the changing values of ${}^a\text{HCO}_3$ against time.

(b) The dehydration of CO_2 . The velocity is given by the equation

$$\frac{d^a \text{H}_2\text{CO}_3}{dt} = k_2 a_{\text{H}_2\text{CO}_3} - k_{1a} \text{CO}_2^a \text{H}_2\text{O} \quad (5)$$

This equation may then be integrated and value of k_2 determined experimentally from the changing values of $a_{\text{H}_2\text{CO}_3}$ against time.

2. The pH is > 12 . Reaction 2 then becomes negligible.

(a) Hydration of CO_2 . The velocity is given by the equation

$$-\frac{d^a \text{CO}_2}{dt} = k_3 a_{\text{CO}_2} a_{\text{OH}^-} - k_{1a} \text{HCO}_3^- \quad (6)$$

which may be integrated and the value of the constant k_3 determined experimentally.

(b) Dehydration of CO_2 . At pH > 12 this is insignificant. For this reason the term $k_{1a} \text{HCO}_3^-$ may be neglected in equation 6.

3. The pH is $> 7.5 < 12$. The complete equation 3 must be used. An integral exists but is too cumbersome for practical use.

The Simultaneous Measurement of Cell Permeability to Water and to Dissolved Substances.—M. H. JACOBS (Laboratory of Physiology, University of Pennsylvania). In order that accurate comparisons may be made between the permeability of different cells to the same substance, of the same cell to different substances, and of the same cell to the same substance at different times, it is desirable to define permeability by an appropriate physical constant which has a real quantitative significance under all these conditions. During the past few years "permeability constants" have been fairly extensively employed by several workers in studying the rate of penetration of cells by water. Corresponding constants for dissolved substances, however, being more difficult to obtain, have as yet been little used. The present method permits not only the accurate determination of permeability constants for dissolved substances but at the same time those for water as well. The principle of the method consists in placing a cell in an originally isotonic solution (*e. g.*, sea water in the case of the egg of *Arbacia*) to which a penetrating substance has been added in known amount, and in then measuring the volume changes which occur during the shrinkage of the cell and the subsequent recovery of its original volume. Knowing the initial and the minimum cell volumes and the time required to reach the latter, the values of the two permeability constants in question may immediately be read off from a chart prepared by solving by a numerical method the differential equations which describe the penetration of the solute and of water respectively. The application of this method to published data of Stewart and Jacobs indicates that on fertilization the permeability of the egg of *Arbacia* to ethylene glycol and to water are increased to approximately the same extent. It also indicates that the effect of temperature on the permeability of the unfertilized egg to ethylene glycol is greater than the corresponding effect in the case of water. It is planned to extend the method to a variety of other problems in the field of cell permeability.

Studies on Contraction of Arterioles.—E. R. CLARK, E. L. CLARK and E. A. SWENSON (Laboratory of Anatomy, University of Pennsylvania). In the various types of transparent chambers permanently

installed in the rabbit's ear it has been possible to study the finest cytologic details of bloodvessels and other tissues and the circulatory changes simultaneously in the living mammal. As we described previously (Clark and Clark, *Am. J. Anat.*, 1932, 49, 441) spontaneous rhythmic contractions of arterics and arterioles and of localized parts of such vessels occur normally from 1 to 4 times a minute in the rabbit's ear. Motion pictures have been taken which show these spontaneous contractions, as well as those which occur after stimulation of the animal, in arteries and arterioles of both the original tissue of the ear and of the newly grown (regenerated) vessels. It has been possible to take pictures in which the outlines of the walls and, in many cases, the microscopic details of the walls (endothelial nuclei, adventitial cells and muscle cells) can be clearly seen.

In motion pictures of the original vessels of the ear with their nerve supply intact it has been possible to obtain accurate measurements of the diameters of arterioles and of arteriovenous anastomoses of various sizes, and to show the time consumed in their contractions. Arteriovenous anastomoses with inside diameters of 0.015 to 0.020 mm. contract in approximately $\frac{1}{2}$ second, while the contraction of arterioles from 0.020 to 0.4 mm. inside diameter, consumes an amount of time varying from $1\frac{1}{2}$ seconds in the smaller to 6 seconds in the larger.

The pictures also add to evidence previously presented that the control of the peripheral circulation in the rabbit's ear resides in the arterioles, while the capillaries and venules are passive.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MAY, 1933

ORIGINAL ARTICLES.

II. NIEMANN-PICK'S DISEASE AND OTHER FORMS OF SO-CALLED XANTHOMATOSIS.*

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In 1914 the Berlin pediatrician, Niemann, communicated the following case:

Case Abstract. A girl, aged 17 months, whose parents were Polish Jews, had been sick since the second month of life. At that time the presence of a splenomegaly had been established. The child had always been difficult to feed and did not thrive. She became worse and the abdomen grew larger. She was admitted to the Berlin University Children's Clinic in a very deplorable condition. The skin was lax and pale, the face was pale brown but not icteric. The abdomen was distended, being 50 cm. in circumference. The spleen and liver formed enormous tumors. The lower border of the liver reached almost to the pelvis. There was a slight ascites; the feet and eyelids were edematous. The blood picture was entirely normal, both as regards the cellular elements and the hemoglobin content. Inasmuch as the Wassermann reaction was positive, antisyphilitic treatment was instituted but without success. The congestive phenomena increased, irregular fever and diarrhea appeared and the child succumbed after a 4 weeks' stay in the clinic.

At the *autopsy* there were no signs of congenital lues, but the spleen was very large and was of a very remarkable consistency. Yellowish-white lesions about the size of a lentil, which often became confluent, protruded from the cut surface. Among these there were scattered small areas of the normal splenic substance so that from a distance the cut surface appeared

* The second of the eighth series of Dunham lectures delivered at the Harvard University Medical School, May 5, 1932.

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completely whitish-yellow. The liver was also markedly changed and presented the color and design of an extremely fatty liver. The fairly soft abdominal lymph nodes were only moderately enlarged, but also showed a peculiar yellowish color. The kidneys also were somewhat yellow; the cortex of the suprarenals was strikingly yellow.

The *microscopic examination* showed that the yellow color was due to the deposition of peculiar large, irregularly outlined cells with small round nuclei and many vacuoles. They were so numerous in portions of the spleen, liver and lymph nodes that they completely displaced the normal parenchymatous structure. With Sudan III the cell body was stained dark, dirty red, so that the presence of lipoids was considered.

Niemann correlated his observations with Gaucher's disease and maintained that the primary differentiation from Gaucher's disease consisted in the early age and the rapid and malignant course. He did not arrive at any definite interpretation. He therefore described his observations under the title, "An Unknown Disease Picture."

Clinical Picture. This communication of Niemann is the basis upon which I subsequently developed the concept of that form of the essential internal xanthomatoses which is known in the literature as Niemann-Pick's disease. Since I described the picture of the disease, somewhat more than 15 cases have been reported. The disease seems to be more rare than Gaucher's disease. Like the latter it is a congenital constitutional and familial disease affecting predominantly the female. The predilection for the Jewish race is even more marked in this disease. Enlargement of the liver and spleen, as Niemann observed in his case, is found in the first months of life. The rapid increase in size of the abdomen, the pale and yellowish-brown discoloration of the skin of the parts exposed to light, *i. e.*, the face, arms and scleræ; the slight ascites, the edema and the bronchitis which are the consequences of congestion, are constant manifestations. In contrast to Gaucher's disease, the superficial lymph nodes are moderately to considerably enlarged. The urine contains no pathologic constituents (especially no bile pigments). The statements about the blood picture agree that foreign large elements are absent, even after the injection of adrenalin. The red blood cells are moderately decreased. Occasionally there is a leukocytosis in the late stages and sometimes a leukopenia. The presence of large vacuoles in many lymphocytes and polymorphonuclear leukocytes is remarkable. The number of blood platelets is normal. The Wassermann reaction in the blood and cerebrospinal fluid is usually negative. The blood may be clouded by a lipemia. The cholesterin content of the blood is most markedly elevated (650 mg. per cent) but at times it is approximately normal. There are as yet no statements as to the phosphatid contents of the blood.

In the course of the disease the progressive enlargement of the spleen and liver produces an extraordinarily large abdomen. It is especially striking because of the simultaneous general emaciation. The extraordinary abdominal circumference of 50 cm. in Niemann's case was also attained in other cases. The enlarged spleen and liver

are smooth and hard and there is often but a thin groove between them. As is true of Gaucher's disease, this disease must be differentiated from Hanot's cirrhosis, von Jaksch-Hayem's anemia, acholuric jaundice, as well as from syphilitic enlargement of the liver and spleen in association with an entirely normal blood picture. However, the large vacuoles of the lymphocytes and leukocytes may attain special diagnostic significance.

Complete diagnostic certainty, excluding especially Gaucher's disease, is afforded by the demonstration of the characteristic cells filled with lipid. This can be shown by puncturing the spleen or the bone marrow. Small tissue particles of characteristic structure may be obtained by puncture or one can obtain by biopsy one of the palpable external lymph nodes for microscopic examination.

The picture of the fully developed surviving storage cell of Niemann-Pick's disease in the freshly examined puncture specimen or in a fresh smear from an organ at autopsy is entirely different from the appearance of the fresh Gaucher cell. The latter is uniformly homogeneous with a dull hyalin sheen. On the other hand the large cells of Niemann-Pick's disease are filled with small round droplets in mulberry-like clusters. They shine moderately and are, in general, not doubly refractile. The same marked difference is also present in the stained smear. The protoplasm of the Gaucher cells is peculiarly wrinkled and it is not uncommonly multinuclear. The storage cells in Niemann-Pick's disease have a quite definite and typical honeycomb or foam structure and have mostly one or two, rarely many, nuclei. In the stained smear the vacuoles lie most often at the periphery while the center of the cell body is homogeneous and quite strongly acidophilic (Fig. 1).

After splenectomy there may be a transitory improvement but just as after radiation of the spleen the malignant course is not prevented. The disease leads to death in all cases, at times within a few months after birth and at the latest in the second year. The children generally die with evidence of general exhaustion, sometimes as a result of intercurrent infection.

Necropsy Findings. Even in a 9-month infant the spleen may be of considerable size—310 gm. as against the 250 gm. maximum normally found in adults. It is tough and hard or, when there is a diffuse transformation into a "fat spleen," it is doughy and one can scrape off a red-yellow creamy fluid. The Malpighian corpuscles remain visible. The liver is likewise extraordinarily enlarged. Especially increased weights of the liver (930 gm. in a 20-months-old child and 580 gm. in one of 16 months) are present if the spleen has been previously removed. The liver appears either as a fatty liver, yellow, doughy and with a characteristic scraping of the cut surface, or it is cirrhotic, tough in spots or diffusely, finely granular and grayish-yellow on section.

The external lymph nodes are moderately enlarged and the inter-

nal nodes are considerably enlarged, being 1 to 2 cm. in diameter. They form packets in numerous places around the liver, the head of the pancreas, the hilus of the spleen, the mesentery, etc. They have a varying shade of yellow, often yellow like fat or actually lemon yellow, and have the same fatty scrapings as the spleen and liver.

The bone marrow may also appear strikingly yellow. Likewise the thymus may have the same consistency as the lymph nodes and, like these, appear unusually yellow.

The suprarenals are especially striking. They are, as a rule, quite enlarged, each weighing 10 gm. in a 7-weeks-old infant. The cortex may be prominent because of its width and its especially yellow color, but even the usually grayish area of darker medulla may be colored yellow.

The intestinal mucous membrane may be diffusely yellow and its protruding lymph nodes are especially prominent. The intima of the large arteries may be opaque and pale yellow, as may be the cortex of the kidneys. The pulmonary parenchyma may be marked by a coarse network of yellowish lines which is visible on the surface of the pleura. I found even the ovaries grayish-yellow. Thus you have in Niemann-Pick's disease a "xanthomatosis," an actual yellowish discoloration of the most marked and widespread form. This is all the more striking when, as I have already indicated, the fat of the subcutaneous tissue has almost disappeared and the epicardium and mesentery are almost free of fat tissue.

This widespread yellow coloration of the organs is caused by the deposition of large pale cells. These are as characteristic for Niemann-Pick's disease as are the large pale cells of Gaucher's disease. But opposed to the latter, as I have already shown, are fundamental histologic and microchemical differences, both as regards the individual cell and as regards their arrangement in the internal organs. I have already indicated the differences in the unstained individual cells obtained by splenic or bone marrow puncture or by smears from the organs. I have also indicated the differences in the stained preparations. In sections, the large Niemann-Pick cells always show a well developed weblike or foam structure (Fig. 3). In sections, as in fresh preparations, they are smaller than Gaucher cells. In Gaucher's disease I found an average cell diameter of 84μ for the fresh preparation and 20 to 80μ for sections. In Niemann-Pick's disease, the cells measured 40μ and 20μ to 60μ respectively. In Niemann-Pick's disease the foam cells show a more or less rounded form, but may be either oval or polyhedral. They never approach the variability of the Gaucher cells which, as you have seen, may appear as elongated spindles or as syncytia. In addition there are marked differences in the staining and the microchemical reactions. The lipoplages of Gaucher's disease are stained blue by Mallory's tricolor stain, while those of Niemann-

Pick's disease stain a dirty grayish-blue. All the known fat and lipid reactions, as well as the optical methods, are absent in Gaucher's disease. The foam cells of Niemann-Pick's disease, on the other hand, can be stained, although irregularly, with Sudan III, Scarlet R, Nile blue or Osmic acid. One may also see drops or needles of doubly refractile bodies. The foam cells are completely filled with large dark blue or black droplets. Often a simple hematoxylin-eosin stain suffices to show the droplets in this tint. The chemical reactions of the product of metabolism which is deposited in the large Niemann-Pick cells are essentially those of phosphatids. Microchemically the phosphatid is the basic lipid of the disease. Neutral fats, cholesterol-fatty acid esters, etc., are present in varying amounts and this variability extends not only to the individual organs or parts of organs, but also to individual cases. The chemical analysis of the spleen and liver, according to the Lieb-Epstein method, confirms the extraordinary increase in phosphatids and the absence of kersin. Other investigators (Sobotka, Epstein and Lichtenstein), using another method, have shown in addition the presence of considerable quantities of cholesterol-fatty acid esters and point out particularly the absence of neutral fat.

The very widespread deposition and distribution of the lipid in the large foam cells has been established by histologic and microchemical studies of the organs. The entire splenic pulp, except for tiny rests, is diffusely infiltrated with foam cells. There are no alveolar localizations as in Gaucher's disease. According to my observations, as you will see, it is certain that the sinus and its endothelium can remain unchanged in spite of complete filling of the pulp (Figs. 2 and 3). However, phosphatids are demonstrable in the endothelium and those foam cells which are found free in the sinuses can, insofar as they have not reached there by breaking through, have arisen in the sinus endothelium. But the principal source of the large cell bodies is the reticulum cells. The less marked participation of the sinus endothelium in the formation of Niemann-Pick's cells is no less impressive than their complete inactivity in the development of Gaucher cells. I found the Turnbull reaction negative in the spleen.

In the liver, parenchymal infiltration also reaches an extreme degree. In addition to the cells of the capillary endothelium and the Kupfer cells, the liver cells themselves are also changed into large clear cell bodies (Fig. 4). In the later stages of the disease evidences of trabeculation is the only indication of the normal structure. As in Gaucher's disease, a marked cirrhosis, without biliary duct proliferation but with inclusion of the foam cells in the fibrous tissue, may occur. These foam cells also originate in the endothelium of the liver vessels and come to lie free in the lumen of the portal vein, hepatic arteries and hepatic veins.

The general framework of the lymph nodes remains intact but

the lymphadenoid tissue is replaced by foam cells to a greater or lesser extent. The mother cells are the reticulum cells and the endothelium of the blood and lymph spaces.

Even when the bone marrow appears macroscopically normal, there may be considerable infiltration with foam cells. They form a third cell type in addition to the fat and marrow cells normally present and arise from reticulum cells.

In the thymus the foam cells replace primarily the cortex of the lobules. In addition a considerable number lie in the loose connective tissue between the lobules.

The Smith-Dietrich reaction is strongly positive in the trachea not only in the connective tissue cells and the endothelium of the bloodvessels, but also in the epithelium of the mucosa, in the smooth muscle cells and, above all, in the cartilage cells (Fig. 5).

Of particular interest are the sections of the lung. The alveolar spaces are large or else filled with particularly large foam cells which are derived from the alveolar epithelium. The capillary bed is, in its greatest part, completely plugged by foam cells (Fig. 6). The interlobar, peribronchial and perivascular fibrous tissue is more or less filled with these cells. The foam cells also lie free in the bronchial arteries, less commonly in the pulmonary arteries or veins.

The thyroid sections treated according to the Smith-Dietrich method surprises one by the complete filling of the entire follicular epithelium by black drops and granules, while the colloid remains free. In addition, many small blackened connective tissue cells lie in the interstitial tissues. The epithelium of the tubules and the duct of the salivary glands as well as the cells of the interstitial connective tissue are affected by the deposition of phosphatids.

In the sections of the tongue where the stroma of the papillae and the interstitial connective tissue are filled with foam cells, two findings are particularly noteworthy after Smith-Dietrich staining—first, the not uncommon presence of black filamentary droplets in the muscle tissue and second, in the lingual nerves the complete filling of the enlarged cells of Schwann and the connective tissue cells of the endoneurium with black droplets and granules.

These are also found to a slight extent in the heart muscle cells. In the interstitial cells and the endothelium between the heart muscle cells, they are very numerous.

Foam cells often lie close together in the intima and cells with blackened phosphatid are seen between the elastic fibers of the aorta and pulmonary artery.

Phosphatid deposition in the suprarenals affects, for the greater part, not the cortex but the medulla. The cortical cells contain only a small number of fine black granules. The medulla shows closely packed lipidphages in nests and cords.

The capillary endothelium of the cortex and medulla of the kidney is filled with black granules. The epithelium of the cortex contains

these granules in irregular groups. The epithelium of the medullary canals is less often involved. The displacement of the glomerular loops by foam cells which have arisen from the endothelium makes a striking picture. The epithelium of Bowman's capsule is also involved. Occasionally lipoid casts appear.

In the small and large intestine a large number of foam cells lie in the stroma and between the crypts in the lymph nodes just as in the thymus. The cortical cells have a predilection for the deposition of the lipid. In the smooth muscle cells of the muscularis mucosæ and the circular and longitudinal muscle fibers, there are rows of fine black dots. The ganglion cells and satellite cells in the plexuses of Meissner and Auerbach are completely filled with these droplets.

I need not enter upon the details of the positive findings in the pancreas, urinary bladder, uterus and tubes, and in the interstitial connective tissue and the endothelium of the bloodvessels or in the epithelium of the tubules and islands of the pancreas.

Again the picture of the process in the ovary is worthy of mention. In the medulla there are numerous foam cells, partly arranged in bundles and partly in clumps. In the cortex, however, not only is the epithelium of the primary follicles for the most part markedly blackened, but also the ovules themselves very often contain black droplets and granules (Fig. 7).

In the pituitary body the Smith-Dietrich reaction is positive in the epithelium of the anterior lobe as well as in the markedly enlarged glia cells which in part occupy the posterior lobe.

I shall later refer particularly to the findings in the brain.

The large cell bodies are able to phagocytise both erythrocytes and leukocytes. They also contain nuclear fragments and pigment and in part have a positive iron reaction. This phagocytosis, however, is inconstant, infrequent and without any significance. I have never succeeded in getting a positive Turnbull's blue reaction in the spleen or in any of the other organs in cases of Niemann-Pick's disease.

It is impossible to enumerate all the positive findings of foam cells and points of lipid storage in the body. Even organs which appear grossly unchanged may contain these characteristic foam cells in great numbers. In addition to the enormous infiltration of the parenchyma of the lymphatic hematopoietic organs, the widespread deposition of the material in the capillaries of the lung is particularly outstanding. Extensive areas are completely plugged by foam cells which in part arise from the capillary endothelium itself and in part, however, are filtered out of the blood stream from the other organs. Since the foam cells are never found in the circulating blood stream, even after the injection of adrenalin, the cells must certainly be filtered out very completely by the lung. But the lipid storing cells are widespread in the body, not only in prac-

tically all organs but also in single types of tissue. In this disease the storage takes place not only in the reticulum cells, the endothelial cells and the fixed and wandering cells (so-called local and wandering histiocytes) of the connective tissue, but also epithelial cells of every description and form. For example, lipid may be found in the epithelium of the liver, of the alveoli of the lungs, of the mucous glands of the trachea, the thyroid, the salivary glands, the kidneys, the adrenals, the pancreas, the ovary, the pituitary, and even in cartilage cells, smooth and striated muscle fibers, ganglion cells, glia cells and the cells of Schwann.

Nature of the Disease. The histiocytic system, as far as one may conceive this idea, is therefore in no way exclusively involved in the storage of lipid and in the production of foam cells. All the body tissue elements, connective tissue, muscle tissue, epithelial tissue and nerve tissue, take part in this process. On this account it is impossible to characterize Niemann-Pick's disease as a lipid-histiocytosis or as a reticulosis or as a reticulo-endothelial disease. It is no more a reticulo-endothelial disease than Gaucher's disease. The storage cells of Gaucher's disease are not reticulo-endothelial cells at all. Furthermore, there are only reticulum cells in association with certain locally limited histiocytic forms. The storage cells in Niemann-Pick's disease cover a wider range than that of the reticulo-endothelial system. They spread in all possible directions in all tissues. The histogenesis of the storage cells in Niemann-Pick's disease is much too universal to permit acceptance of the designation "lipoid histiocytosis."

Since in Niemann-Pick's disease cells of all the body tissues are involved, it appears really necessary to explain the disease upon a single composite basis and not, for example, to limit it to a primary insufficiency of the reticulo-endothelial apparatus. Here, also, therefore, the pathogenesis revolves itself upon a primary metabolic disorder which leads to an overloading of the blood stream and the tissues with lipoids, especially with phosphatids. At the same time a marked disappearance of the stored neutral fat takes place. The foreign material in the blood stream and tissue fluids first of all mobilizes the entire histiocytic apparatus, mainly the spleen, the liver, the lymph nodes and the bone marrow.

In infancy, however, as I have shown, the macrophage system is widespread and on this account the lipid storage takes place in many other localizations and in various other organs, after the natural storage localizations are overloaded. At this point the systematization ends. The excess amount of the material present then forces the parenchymal cells, and even the cartilage cells, to store the substance. This results not only in extraordinary sites of localization but also widespread parenchymal damage. Vital functions of various organs are hindered and the result is a premature death due to cachexia.

This concept of the pathogenesis leads to an easy understanding of the clinical and anatomic contrast of Niemann-Pick's and Gaucher's disease. In Gaucher's disease it is the ultrachronic course which contributes to the fixity of the tissue reactions and the localization of the diseased process. In the Niemann-Pick disease the qualitative and the quantitative intensity of the foreign chemical stimulus leads to a very precipitate reaction; hence the unusual diffuse and widespread lipid infiltration of the organs, the early, rapid and excessive enlargement of the spleen and liver and the early death through the destruction of vital functions. Gaucher's disease can cause death in infancy or childhood with the full blown picture of the disease present, but in Niemann-Pick's disease, death *must* occur in infancy or childhood because the parenchymal cells lose their function and the vital organs are overwhelmingly infiltrated with lipid cells.

As in Gaucher's disease the cause of this disturbance in metabolism is not understood. It is no more than a hypothesis to assume, for instance, that an endocrine factor is concerned. Sobotka emphasizes the lack of neutral fat in all the organs. This is consistent with the macroscopic and microscopic postmortem findings. He believes that there is a dysfunction of the spleen, liver, lymph nodes, bone marrow, etc. The physiologic function, concerned in the conversion of lecithin- and cholesterol-fatty acid esters into neutral fat, is lost in those cells which participate in the process of fat metabolism. It is possible that enzymes normally associated with this process of esterolysis are lacking. This theory requires further confirmation.

Relation to Tay-Sachs' Disease. However, according to my investigations, Niemann-Pick's disease has an important practical and theoretical relationship to another disease of infancy, namely to amaurotic family idiocy and especially to that type which runs the most rapid course, namely Tay-Sachs' disease. I have found Tay-Sachs' amaurotic family idiocy combined with Niemann-Pick's disease and this combination has been confirmed in some of the later reports. Tay-Sachs' disease is also, as is well known, a disease that is strictly familial and affects exclusively the Jewish race; it causes blindness and leads to death by destruction of all cerebral functions.

In association with Max Bielschowsky, I have demonstrated the complete histologic identity between the cellular changes in the cerebrum in Tay-Sachs' and in Niemann-Pick's disease. At the same time, we also noted a spread of the foam cells in the leptomeninges in the tela choroidea and in the connective tissue about the cerebral vessels, corresponding to the generalized spread of the foam cells in the connective tissue and the wall of the bloodvessels in Niemann-Pick's disease.

Clinical Abstract. In the first autopsy that I performed upon a case of Niemann-Pick's disease, the clinical manifestations pointed to an involve-

ment of the cerebrum. This child, aged 14 months, upon admission to the University Children's Clinic in Berlin, lay motionless in bed and could not keep its head erect. The patellar and Achilles reflexes were absent, the child could fix and follow objects placed before the eyes but could not readily grasp such objects. The left pupil was smaller than the right and did not react to light. The child slowly became apathetic. This apathy, in association with the motor manifestations, suggested the possibility of Tay-Sachs' disease. The assumption became certain after the ophthalmologic examination. The retina in the region of the macula lutea was colored gray and in the fovea centralis there was found the typical cherry-red spot.

At the autopsy I found the brain unusually firm, which was especially striking in view of the usual soft consistency of the average brain in infants. The organ maintained its shape upon the autopsy table, the convolutions were narrow, and the fissures were deep.

Microscopic examination of sections of the central nervous system revealed a storage of lipoid substance in the ganglia and glia cells, which morphologically and tinctorially were identical not only with those in the other body organs but also with those which are usually found in the nerve and glia cells in Tay-Sachs' amaurotic idiocy.

The lipoid storage involves, in one disease as in the other, the brain cortex, the spinal cord and the spinal ganglia. The identity of the changes is evidenced not only in the cellular storage itself but even in the tissue arrangement of the storage cells.

A section through brain cortex, for instance in the region of the precentral gyrus, shows all the ganglion cells to stand out a deep black when lipoid stains are employed while they normally appear shadowy and gray-blue. At the same time innumerable glia cells are intensely blackened and their cell bodies are swollen by the stored lipoid (Fig. 8). The blackening of the cells is furthermore no less marked in the cortex of the cerebellum. The layer of Purkinje cells is clearly demarcated from the neighboring molecular layer and the granular layer of the cerebellar cortex because the Purkinje cells contain a large amount of the blackened substance (Figs. 9 and 10). One sees in many Purkinje cells a balloon-like swelling of the dendrites caused by lipoid deposition. All these pictures occur frequently in the histopathology of Tay-Sachs' disease (Fig. 11). There is a further cerebral histopathologic similarity with Tay-Sachs' disease, namely, the delay or cessation in the maturation of definite nerve fiber tracts which in the normal development become medullated late in fetal life. In our cases the developmental anomaly affects chiefly the white substance of the temporal lobe and the lateral portion of the centrum semiovale. Other nerve fiber tracts are entirely unaffected.

In contrast to the findings in Tay-Sachs' disease, one finds a marked lipoid deposition in the entire connective tissue and perivascular apparatus of the brain. That corresponds, as I have already pointed out, to the universal occurrence of lipoid phagocytes in Niemann-Pick's disease.

In any case the fact remains that the infantile Tay-Sachs' disease and Niemann-Pick's disease are related in their typical clinical and

anatomic picture. This fact is in strong support of the concept of those authors who regard the essential disturbance in Tay-Sachs' disease as being a metabolic disturbance of a diseased nervous tissue.

The identity of the histologic findings leads directly to the concept which I have presented with Max Bielschowsky, that Tay-Sachs' disease has its basis in the same metabolic disturbance as in Niemann-Pick's disease—that is, it is a localization in one organ of this general disturbance of lipoid metabolism. It is true that the majority of the cases of Tay-Sachs' disease do not present clinically a hepatosplenomegaly and, furthermore, it has not yet been shown that the cellular and tissue changes of Tay-Sachs' disease occur in *all* cases of Niemann-Pick's lipoid storage. In the internal organs, for example in the spleen, were found pictures in juvenile amaurotic idiocy, which correspond completely with those in Niemann-Pick's disease (Fig. 12).

From all of this it follows, and I will express myself very cautiously, that the cellular changes in Tay-Sachs' disease are primarily conditioned by a metabolic disturbance which leads to lipoid deposition in the ganglia and glia cells and that this metabolic disturbance in infantile Tay-Sachs' disease must be of the same kind as that in Niemann-Pick's disease.

Finally, it must be stated that in the infantile form of Gaucher's disease, lipoid corresponding microchemically and optically to Gaucher substance is often deposited in the cerebral cortex. Except for the differences in the character of the deposited lipoids, the resemblance with the ganglion cell pictures seen in Tay-Sachs' disease is striking. This fundamental similarity in the involvement of the elements of the central nervous system in Gaucher's disease, as well as in Niemann-Pick's disease speaks against a mere accidental combination of the two diseases and is even more indication of a primary disturbance of the lipoid metabolism affecting the ganglion cells in both diseases. I have gone in detail into these questions because here the pathologic-anatomic study of a metabolic disease has opened a pathway which may explain the pathogenesis of a cerebral disease which hitherto has been a mystery.

Hand-Schüller-Christian's Disease. To complete the description of the essential general xanthomatoses, it is necessary to describe both this disease and the group of essential irregularly localized forms. I can limit myself somewhat inasmuch as the cases of xanthomatoses with varying localizations do not present a constant clinical anatomic picture of Hand-Schüller-Christian's disease which was, as you know, first investigated in your country (Philadelphia and Boston). We are indebted to R. S. Rowland not only for a complete clinical anatomic presentation of the disease, but also for the important knowledge that this disease belongs to the essential xanthomatoses.

Like Gaucher's disease and Niemann-Pick's disease, Hand-

Schüller-Christian's disease is also a congenital familial disease on a constitutional basis. It occurs predominantly in Jews and, as far as we know, in the male sex. The lipid deposition here consists chiefly of cholesterol-fatty acid esters. The accumulation of large storage cells is secondary to a very characteristic granulation tissue which has an outspoken tendency to conversion into fibrous scars.

Clinical Picture. The first symptoms of this disease begin in the second year. In most instances there is a very characteristic triad of symptoms: (1) defects of the bones, especially of the skull; (2) exophthalmos and (3) diabetes insipidus. In addition there is a growth disturbance, changes as in dystrophia adiposogenitalis, yellow-brown discoloration of the skin, dyspnea and cyanosis and often also moderate enlargement of the liver, spleen and lymph nodes.

The course can be a mild one, interrupted by remissions, and death may be delayed until the third decade of life, unless occasioned earlier by an intercurrent disease. The cholesterol, phosphatids and fatty acids of the blood are increased. However, during the remissions the values approach the normal. Lipemia has not been observed.

In the differential diagnosis the bony defects have primarily to be considered. Gaucher's disease, syphilis, tuberculosis, multiple myeloma, osteitis fibrosa cystica and neoplasms have to be ruled out. The presence of the radiographically characteristic defects of the skull (geographic skull) speaks in favor of Hand-Schüller-Christian's disease. However, as in Gaucher's and Niemann-Pick's disease, only the demonstration of the characteristic storage cells (foam cells) in biopsy makes the diagnosis certain.

I have my doubts whether dietary or endocrine therapy can be effective. It is true that radiation causes rapid regeneration. However, even during the treatment, new foci develop. In protracted cases bony defects may heal spontaneously.

Pathologic Anatomy. An autopsy of a fully developed case of Hand-Schüller-Christian's disease presents the distinct picture of a disease of the skeleton, particularly of the skull. Within the convexity and in the base of the skull there are numerous defects of varying shape and size. They are filled by a light yellow or brownish granulomatous tough substance, which originates in the dura or simultaneously in the periosteum. In later stages of the disease the granuloma becomes a cicatricial fibrous tissue, also of yellow tint. Occasionally cysts develop and these contain yellowish or reddish-brown semifluid material. The yellow granulomatous tissue invades the orbits, the accessory nasal sinuses and the mastoid cells and pushes the pituitary gland upward. The pituitary gland proper and the structures in the near vicinity at the floor of the third ventricle may appear diffusely yellow. The other organs are involved



FIG. 1.

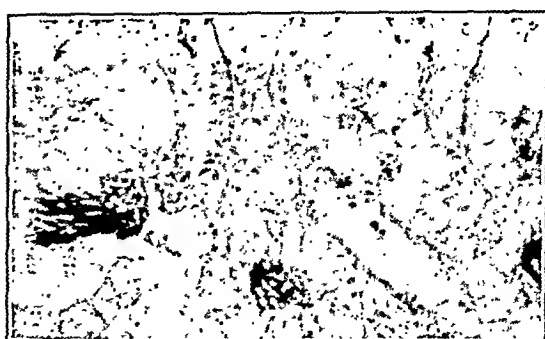


FIG. 2.

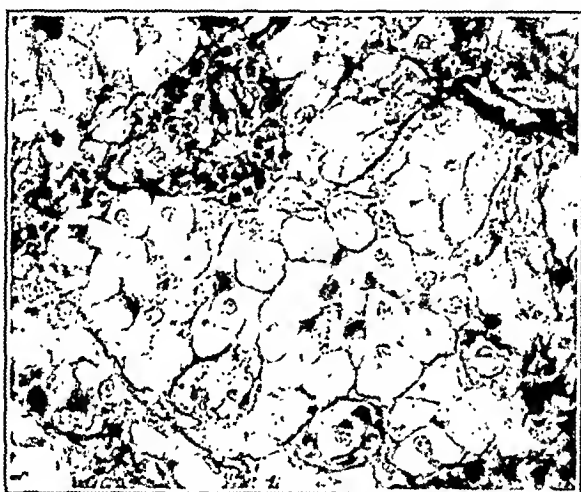


FIG. 3.

FIG. 1.—Smear of cells from splenic puncture in Niemann-Pick's disease. Note typical cell with vacuoles peripherally located with homogeneous center.

FIG. 2.—Section of spleen in Niemann-Pick's disease. The sinus endothelium is free of lipid. Hematoxylin and eosin

FIG. 3.—Section of spleen in Niemann-Pick's disease. Typical vacuolated storage cells. Hematoxylin and eosin.

FIG. 4.—Section of liver in Niemann-Pick's disease. Note blackening of phosphatids stored in endothelial, Kupffer and liver epithelial cells. Smith-Dietrich stain.

FIG. 5.—Cartilage of trachea in Niemann-Pick's disease. Blackened phosphatids in cartilage cells. Smith-Dietrich stain.

FIG. 6.—Section of lung in Niemann-Pick's disease. Note dilatation and blockage of pulmonary capillaries by vacuolated storage cells. Hematoxylin and eosin.

FIG. 7.—Ovarian cortex in Niemann-Pick's disease. Striking demarcation of the epithelial cells of the primordial follicles and ovulum proper. Smith-Dietrich stain.

FIG. 8.—Section of "precentral gyrus" of brain in Niemann-Pick's disease. Blackened phosphatids in ganglion and glial cells. Smith-Dietrich stain.

FIG. 9.—Section of cerebellum in Niemann-Pick's disease. Striking demarcation caused by blackened phosphatids in Purkinje cells. Smith-Dietrich stain.

FIG. 10.—Purkinje cells in Niemann-Pick's disease. Lipoid stains light. Bielschowsky stain.

FIG. 11.—Purkinje cells in Niemann-Pick's disease. Lipoid stains light. Balloon-like swelling of a dendrite. Bielschowsky stain.

FIG. 12.—Section of spleen in juvenile type of Tay-Sachs' disease (amaurotic family idiocy). Phosphatid-storing cells in splenic pulp corresponding to storage cells in Niemann-Pick's disease. Hematoxylin and eosin.



FIG. 4.



FIG. 5.



FIG. 6.



FIG. 7.

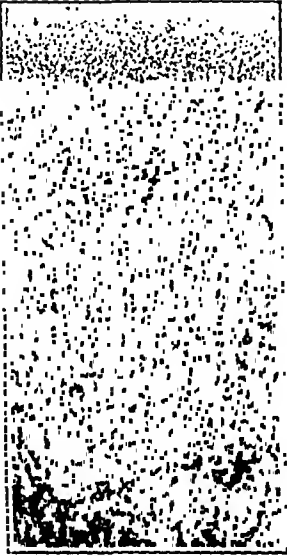


FIG. 8.



FIG. 9.



FIG 10.

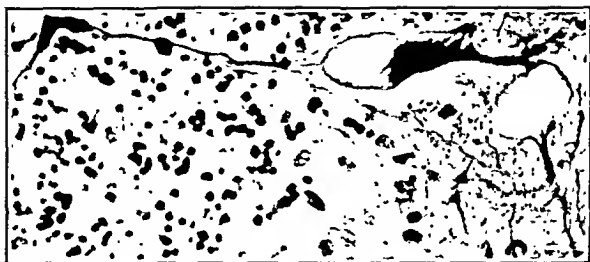


FIG. 11.

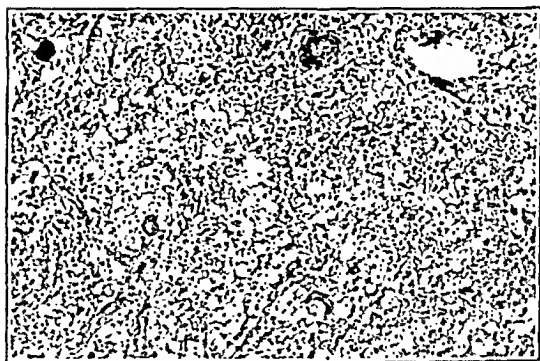


FIG. 12.

only occasionally. The spleen, liver, lymph nodes and also the kidneys may be moderately enlarged and diffusely yellow-stained. The bone marrow, too, shows not infrequently a diffuse or patchy yellow color. The same holds true for the thymus, tonsils, wall of the esophagus and stomach, Peyer's patches, heart and walls of the large vessels. It is striking that the adrenals with yellow cortex may be found reduced in size and that the yellowish speckled lung is often conspicuously firm.

The foam cells vary in size and shape and commonly resemble the type found in secondary xanthoma. They include one or two small nuclei, occasionally even many, and because of their prevailing cholesterol content they are well stained with Sudan and Nile blue and are doubly refractile. Frequently they contain cystalline needles or small rods. They may be freed from disintegrated cells and cause the appearance of multinucleated foreign body giant cells. The chemical analysis of the organs reveals also a preponderance in the figures of cholesterol and its esters over the phosphatids and neutral fats.

Groups of round and eosinophilic cells are found in combination with the foam cells and suggest the appearance of a granulation tissue. In addition there occur hemorrhages and necroses. The fibrous cicatricial transformation is initiated by the proliferation of numerous spindle cells arranged in bundles. Within the fibrillar scar tissue, giant cells and numerous cholesterol needles or plates are retained for a long time.

As far as their origin is concerned, Rowland summarily characterizes the foam cells as derivatives of the reticulo-endothelial cells or histiocytes. As far as I can see, only their origin from reticulum cells and from histiocytes of the adventitia and the perivascular connective tissues is established. According to Rowland the parenchymal cells of the glandular organs and certain other tissues participate in addition in the lipoid deposition. This is analogous to Niemann-Pick's disease, although the storage is not as intense.

The foam cells are also widely distributed in organs which do not show macroscopic alterations. They lie within the connective tissue, as in the near vicinity of small blood and lymph vessels, and cause, if present in the larger groups, the grossly recognizable yellow color. Again the tendency to fibrous transformation, *i. e.*, to cicatrization, is very conspicuous, especially within the liver. It is most marked within the lungs where the proliferating connective tissue between the alveoli causes their obliteration. The fibrosis is responsible for the induration of the lungs, the dyspnea and cyanosis, and predisposes the organ to pneumonia.

The complete replacement of the bone marrow by the masses of foam cells and the subsequent formation of the granulomatous tissue is the cause of the bony defects. The embarrassment of the circulation results in small resorbable necroses of the bony substance

which can be termed *caries sicca xanthomatosa*. Extensive replacement of the bone marrow causes severe fatal anemia by myelophthisis. The exophthalmos is the result of granulomatous masses which have invaded the orbit. The diabetes insipidus as well as the general developmental retardation and the dystrophia adiposogenitalis are symptoms of the involvement of the pituitary gland, which has not only been displaced by the granulation tissue but in addition has been infiltrated by foam cells. The same takes place in the infundibulum and the tuber cinereum.

In this way all the clinical features of the disease find their full explanation in their anatomic-histologic counterparts.

The fourth and last group of the essential xanthomatoses is a residual group. Whatever remains after Gaucher's disease, Niemann-Pick's disease and Hand-Schüller-Christian's disease have been eliminated belongs to this group. It corresponds entirely in its varying localization and in its histology, and as far as our knowledge goes also in its chemistry, to the symptomatic xanthomatoses, except that a fundamental disease is absent. Here also, the chief component of the lipid deposition is probably cholesterol. I have already mentioned that the variation in the localization of these xanthomatoses accounts for the fact that there does not exist a precise clinical-anatomic picture. The skin and internal organs may be involved by the xanthomatous deposits to a varying degree. It seems, however, as if one might still be able to separate still another well circumscribed type which represents again a disease of the bones and which presents a possible characteristic Roentgen ray picture. William Chester, working under Erdheim, first reported two observations of this type. Subsequently a few cases, identical in their clinical, radiologic and pathologic-anatomic aspects, have been observed and I also can show you such a case.

They are apparently not characteristic for any definite age period and occur in men and women. As in Hand-Schüller-Christian's disease, the widespread deposition of lipid containing cells within the bone marrow, widely distributed all over the skeletal system, passes into a lipid granulomatosis. But instead of the skull being the chief seat of the disease, it is more conspicuous in the diaphyses of the long bones; and the fibrous healing stage which occurs in the lipid granulomata does not result in bony defects but provokes an osteoplastic reaction, *i. e.*, extensive new formation of bony substance. The bones are externally unaltered and the periosteum is free. The deposits of lipid granulomata appear on cross-section in part as yellow foci and in part they occupy longer areas of the marrow cavity. The microscope reveals a porosity of the compacta and of the spongiosa of the bones, caused by either recent or older cicatrizing lipid granuloma. Near it, however, there is an entirely "unstatic," independently new "irritation spongiosa" with slender

bone trabeculae between the bony substance. The foci of lipoid granulomata which tend to heal with fibrosis are delimited by special bony marginal trabeculae. Occasionally, as in some of the reported instances, a dense osteosclerosis may occur, particularly at the distal portions of the femur and the diaphysis of the tibia, which gives a dense Roentgen ray shadow. Xanthomatosis of the skin or of the internal organs may be present or absent, in accordance with the variability of the organic involvement characteristic for this group. It may be sufficient to characterize these cases of peculiar bony xanthomatoses as separate entities. We are just beginning to collect our observations and experiences. It is mainly necessary to investigate the type of the deposited lipoid and the lipoid contents of the blood.

It must be considered that cases of this type deserve the term "lipoid granuloma" in a secondary sense only. The granulomata do not develop primarily with subsequent lipoid storage within their cells but, conversely, the primary process is the deposition of storage cells within the bone marrow. From this, as in Hand-Schüller-Christian's disease, the lipoid granuloma develops. It is absolutely untenable, and this must be emphasized, to include Niemann-Pick's disease among the lipoid granulomata. In this instance there never exists in any phase, a lipoid cellular granulation tissue or anything which is even remotely related.

The knowledge of the generalized essential xanthomatoses is still recent in its present classification. The important information regarding the nature of Gaucher's, Niemann-Pick's and Hand-Schüller-Christian's diseases dates back only to the last decade. There is, however, no doubt in regard to the principal differences among these three affections.

The separation of these three storage diseases from one another is the more certain because the differentiation is not only clinical and anatomic but also chemical. Gaucher's disease stores mainly kersin, Niemann-Pick's phosphatids and Hand-Schüller-Christian's disease, cholesterol. It is true that certain features are common to all three diseases. In common there is a familial congenital disturbance of the lipoid metabolism on a constitutional basis and this aberration shows predilection for the Jewish race. The reason for this is probably the coincidence of the determining hereditary factors favored by frequent blood marriages. All three diseases are accompanied by hemachromatosis with yellowish-brown pigmentation of the exposed skin. In all three diseases, disappearance of the storage cells may occur with subsequent formation of fibrous scars. Gaucher's and Hand-Schüller-Christian's disease exhibit surprisingly independent localization of lipoid storage within the skeletal system. This occurs apparently in still another form which is at present still classified among the unnamed essential xanthomatoses.

Yet there is, aside from this fundamental agreement, almost always a particular characteristic for each disease entity. Gaucher's disease and Niemann-Pick's disease predominate in the female sex; Hand-Schüller-Christian's disease predominates in the male sex, as far as the existing observations show. In Gaucher's disease and in Niemann-Pick's disease the cicatricial new formations develop in the liver with the disappearance of the storage cells directly by a sort of insidious condensation of the fibrous stroma. In Hand-Schüller-Christian's disease, however, and also in the unnamed bone xanthomatoses there is granulation tissue formation. In Gaucher's disease the osseous form of the disease is exceptional. In Hand-Schüller-Christian's disease, and of course also in the unnamed bone xanthomatoses, it is the rule and the leading symptom. In Hand-Schüller-Christian's disease the skull is involved primarily; in Gaucher's disease and in the bone xanthomatoses, the entire skeleton. As you see, there are clinical-anatomic differences in all the groups.

Objection has been raised against the classification of the generalized essential xanthomatoses or lipoidoses with the three named diseases. It has been claimed that there are instances which altogether do not belong in this system and that cases have been observed which take an intermediary position, as the observation of Hamperl and Dienst who found, in the organs of the type Niemann-Pick, a small amount of kersin in addition to the abundant phosphatids. Such observations do not invalidate the classification by any means but corroborate it, because they tend to confirm what was to be expected *a priori*. One should not forget Aristotle's words: *Natura non saltum facit*. All natural phenomena necessarily show such transitions. I have repeatedly emphasized that there exists a number of variations in addition to the classical disease entities of the generalized essential xanthomatoses which do not fit the scheme and which have occasionally a distinctly uncertain character. I have compiled and reported such cases. Most probably the system in its present form is not even complete.

Thus, the recent teaching of the generalized essential xanthomatoses appears to be well founded in its fundamentals. The system has proven its practical utility in a sufficient number of cases. I hope, from what I have discussed and demonstrated, that you have gained this belief and that you now see before you the pathway which further investigation has to pursue.

If much of our knowledge is still incomplete in structure and content and perhaps must remain so, then you must recall the words of the famous scientist, Karl Ernst von Baer:

"Science is eternal in its sources,
Boundless in extent,
Infinite in structure,
Unattainable in purpose."

STUDIES ON THE STRUCTURE AND FUNCTION OF BONE MARROW.

III. BONE MARROW BIOPSY.

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A quarter century has passed since Ghedini, of Genoa, performed the first biopsy of bone marrow (1908) and subsequently (1910, 1911) described the technique and the results of his studies. The medical profession, usually alert for new means of diagnosis and study, has not received the procedure with favor; mute evidence lies in the fact that, since the time of Ghedini, hardly a dozen articles related to such study have appeared. Recently Hellwig, in an excellent comprehensive review of biopsy, totally neglected to mention biopsy of the bone marrow. From this lack of interest one might infer that the results of the procedure do not justify its performance; a survey of past work and our experience thus far are not in accordance with such inference.

Most authors have been content with study of smears of material aspirated by various means from the myeloid cavity—Ghedini, Zadek (1921, 1922), Morris and Faleoner (1922), Seyfarth (1923), Arinkin (1928), Arjeff (1931), Tuschinsky and Kotlarenko (1932), and Sokolowski (1932). Peabody alone (1927) was concerned with carefully prepared sections of eurented marrow tissue. Smears are of distinct value for comparison of marrow cells with cells of the circulating blood, preparation and staining technique being alike; used alone, however, the limitations of smears are obvious. Quoting Peabody, "they do not necessarily give the correct idea of the relative number of different cell types present (thus megaloblasts may be so firmly adherent to one another that only a small proportion appears in the smear), and they give no indication of the actual structure of the bone marrow. As more is learned about the normal physiology of blood formation and the liberation of cells into the peripheral vessels, it becomes apparent that these physiologic functions can often be interpreted by the study of the anatomy of the bone marrow. It is thus evident that the elucidation of the pathologic physiology of the diseases of the hematopoietic system will be considerably aided by a better knowledge of the structure of the bone marrow, which can be acquired only from the study of sections of fixed tissue." Going further, invaluable information

regarding the cell elements of the marrow may be obtained through tissue culture and supravital stained preparations that can never be gained through study of dead cells.

The purpose of this paper is to outline in detail a technique for bone marrow biopsy, the use of which will furnish uniformly good marrow preparations in a comparatively short time, and to describe briefly a method for study of the preparations thus obtained. It is hoped that the use of the procedure for diagnosis and study of disease of the hemolytotoxic system will be stimulated.

Selection of Site for Biopsy. Earlier observers (Ghedini, Morris and Falconer, Zadek, Peabody) performed biopsy on the tibia. It was pointed out in a previous paper³ that the tibial marrow loses its hemopoietic elements during the adolescent and early adult period and becomes practically entirely fatty; further, that only under the most extreme stimulation, as in untreated pernicious anemia in phases of relapse, does the metamorphosis to red marrow occur; far less labile is the tibia than the femur, for example. This is demonstrated graphically in the charts presented in the preceding paper of this series.⁴ Peabody has stated: "The marrow of the tibia, which may be involved only rather late, is nevertheless, a more sensitive index of the extent and degree of the pathologic process (*i. e.*, referring to pernicious anemia) than is, for instance, the marrow of the femur." On the contrary, the author considers the tibial marrow one of the coarsest indices of hemopoietic response, even though it be true that the earliest stages of a pathologic process involving the blood-forming organs may be more readily followed in the relatively simple marrow of this bone than in the complex myeloid tissue of the spongy bones. When blood-forming tissue is found here, it indicates a most extreme hemopoietic reaction. How often, though, does one perform biopsy on the tibia, only to be rewarded by a section of simple, practically acellular fat to study? Or worse, what is the interpretation of such a find by one unfamiliar with the variation in cellularity in the different bones? Within the past few months the author has known the unjustified diagnosis of aplastic anemia to be made in 2 cases, largely on the ground of a fatty tibial marrow; fortunately such instances are uncommon.

The femoral marrow, regarded as the most useful single marrow for postmortem study, is not available for biopsy for obvious reasons. The sternum offers far more hope for an adequate cytologic study of the marrow; it remains cellular in part throughout life, although fat content increases with advancing age. The bone is readily accessible and trephine is accomplished with much less difficulty than through the thick, dense cortex of the tibia. Perhaps the optimum state would be obtained through examination of both bones simultaneously, but seldom would either patient or clinician feel this justified. Of the 2 available bones, then, the sternum seems preferable for biopsy.

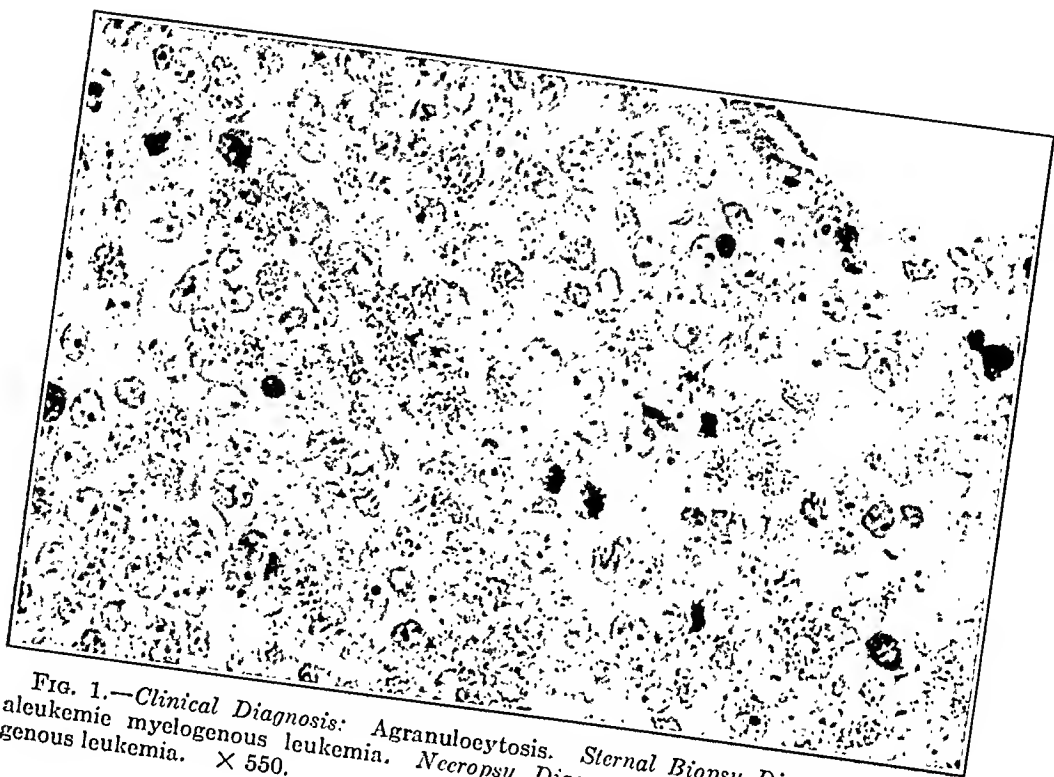


FIG. 1.—*Clinical Diagnosis:* Agranulocytosis. *Sternal Biopsy Diagnosis:* Acute aleukemic myelogenous leukemia. *Necropsy Diagnosis:* Acute aleukemic myelogenous leukemia. $\times 550$.

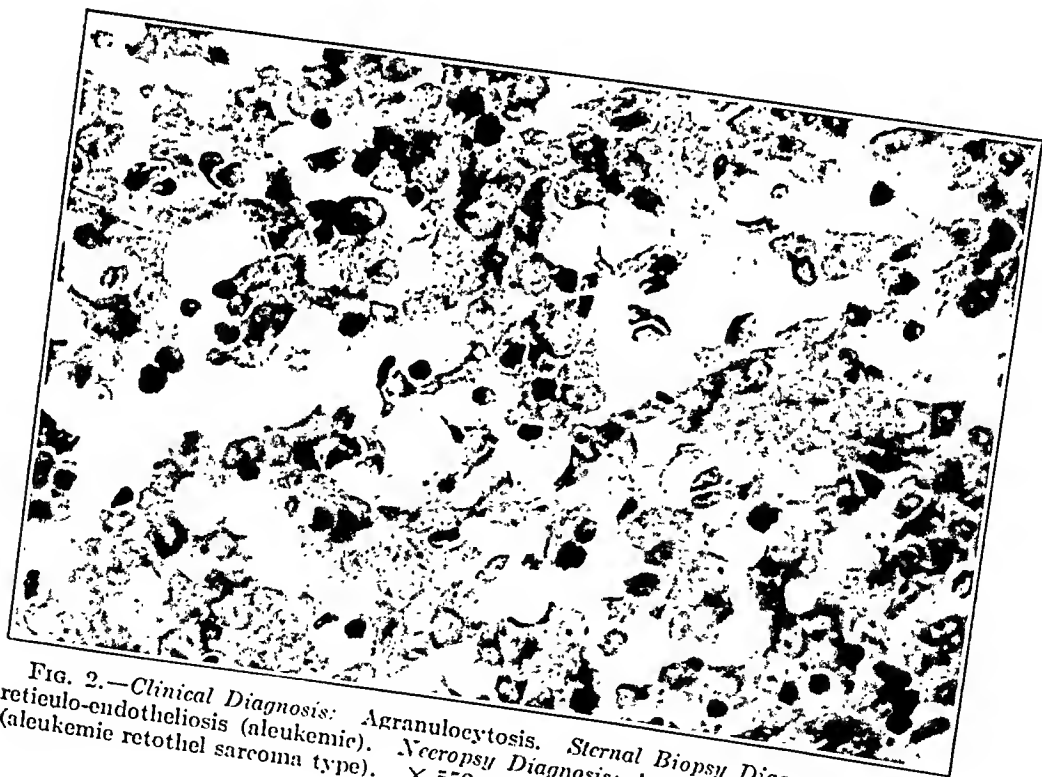
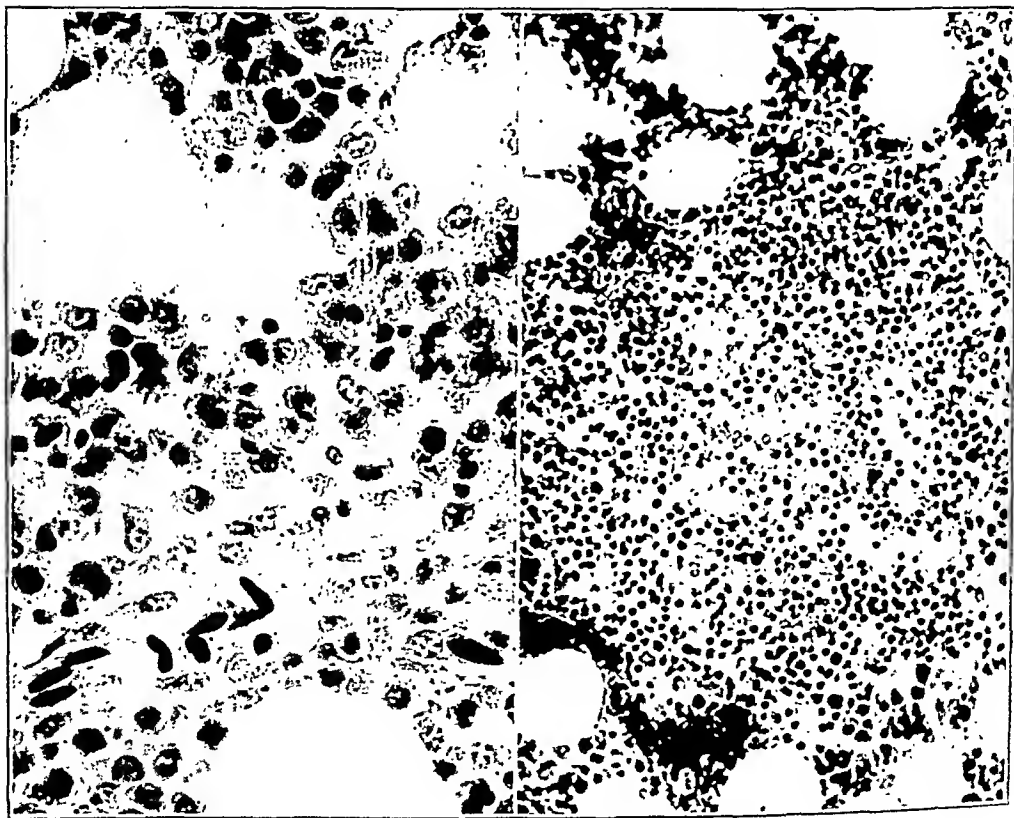


FIG. 2.—*Clinical Diagnosis:* Agranulocytosis. *Sternal Biopsy Diagnosis:* Acute reticulo-endotheliosis (aleukemic). *Necropsy Diagnosis:* Acute reticulo-endotheliosis (aleukemic reticthel sarcoma type). $\times 550$.



FIG. 3.—*Clinical Diagnosis:* Agranulocytosis *Sternal Biopsy Diagnosis:* Aplastic anemia. *Necropsy Diagnosis:* Aplastic anemia. $\times 550$.



A

B

FIG. 4.—Characteristic sternal marrow picture of the *disease* agranulocytosis (not the *syndrome*) (to be described in detail in a subsequent article). A, myeloblastic hyperplasia with maturation defect; normal erythropoiesis ($\times 550$); B, focal necrosis with lymphocyte response ($\times 41$).

Surgical Technique. Some authors have advocated needle biopsy of the sternum and have described a variety of methods and instruments for its performance. The chief disadvantage lies in the fact that only aspirated marrow is available for study, thus rendering impossible section of fixed myeloid tissue in which cytologic relations are maintained. Morris and Paleoner devised an electric drill for trephining bone; we found no such elaborate instrument necessary. The following surgical technique for the removal of a sternal button has been adopted:

Using *rigid* aseptic precautions, the skin and subcutaneous tissue are infiltrated at least 1.5 cm. to right and left of the midline with a 2 per cent solution of novocain for a distance of 3 cm. above and below the attachment of the fourth rib. After a lapse of 5 minutes a sagittal incision, 4 cm. in length, is made down to, but not including, periosteum. The needle is inserted beneath the periosteum and the subperiosteal space is infiltrated with novocain over the operative field; thus all sensitive parts have been rendered anesthetic. The periosteum is incised in the line of skin incision and elevated, exposing an area slightly greater than 1 cm. in diameter. Using an ordinary trephine of 1 cm. diameter, the ventral table of the sternum is cut; the marrow cavity has been entered when the sensation of a slight downward thrust is experienced (care must be exerted not to continue drilling through dorsal table into mediastinum).^{*} The trephine is tilted slightly back and forth in sagittal and transverse planes, thus breaking the fine trabeculae of the underlying cancellous bone. The trephine is withdrawn; the bone button will come away with the drill or can be removed with tissue forceps. The margin and floor of the myeloid cavity are scraped with a sharp bone curette; the curettings and button are handed to the pathologist (whose presence at operation is imperative) on a sterile sponge. The cavity is packed firmly with gauze until all oozing has ceased; the periosteum is replaced over the bone defect, but not sutured; skin and subcutaneous tissue are approximated with interrupted No. 00 plain catgut (or horsehair) sutures (in female subjects a carefully laid subcuticular suture may be preferable). Sterile dressings are applied and the patient returned to bed; dressings may be discontinued after the sutures have been absorbed (usually about the sixth day). There is eventual fibrous or osseous replacement of the bone defect and the resulting scar an inconspicuous, fine, white line.

Microscopic Technique. A tiny fragment of the curettings should be teased out and stained supravitaly according to the technique of Doan or Forkner. If tissue cultures are to be made, the marrow fragment should be placed in the medium as soon after removal as

^{*} As an added precaution against entering the mediastinum, a mark can be made on the trephine 5 mm. from the cutting edge; drilling should stop when this mark is reached.

possible (the technique of Maximow or of Lewis is preferable). Smears should be made from the curettings as directed,³ both wet-fixed and dry, stained by the method used on blood films from the patient (May-Grünwald-Giemsa, acetone-Giemsa or Wright's are best). Thus a comparison of the cytology of peripheral blood and blood-forming organs is possible.

The button and remaining curettings are fixed promptly in Zenker-formol solution for 4 to 6 hours, washed for an equivalent length of time in running water and decalcified in a solution of equal parts of 85 per cent formic acid and 20 per cent sodium citrate (6 hours is usually sufficient, although the tissue may be left overnight without destroying the staining quality of the cells). The tissue is washed in running water for about 4 hours, transferred through 95 per cent alcohol (12 hours), absolute alcohol (6 hours), chloroform (45 minutes), chloroform and paraffin (30 minutes in oven), paraffin (40 to 42° C.) (15 to 20 minutes), paraffin (53° to 56° C.) (2 changes totalling 30 minutes) and finally embedded in paraffin, being careful to embed the button with the marrow surface downward. The tissue is blocked and cut in the usual fashion, preferably not over 5 micra in thickness, mounted on albuminized slides and placed in the oven for at least 2 hours (better overnight to insure flat sections). Paraffin is removed by 2 changes of xylol, following which the slides are transferred through the following solutions: 95 per cent alcohol, 95 per cent alcohol and iodine (cherry-red solution) until the mercury of the fixative is removed, 95, 70, 50 and 30 per cent alcohol and finally through 3 changes of distilled water to insure removal of all alcohol. Slides are then placed in the stain mixture prepared as follows:

<i>Solution I.</i>	
Eosin für Blut (Grübler)	1 gm.
Distilled water	1 liter

<i>Solution II</i>	
Azure II	1 gm
Distilled water	1 liter

(Azure II as supplied by National Aniline and Chemical Company only.)

Mix solutions as follows in the indicated order:

1. Distilled water	50 cc.
2. Solution I	20 cc.
3. Solution II	10 cc.

Stain from late afternoon until the following morning. Differentiate, controlling differentiation under the microscope:

1. Alcohol, 95 per cent, until blue stain ceases to come off in a cloud.

2. Alcohol, 95 per cent, until differentiation is complete (bone trabeculae, red blood cells, eosinophil granules are the landmarks and should be red; nuclei should be sharp and brilliant blue).

3. Transfer rapidly through 2 changes of absolute alcohol for dehydration.

4. Xylol (3 changes) until clear. At this time check stain under high dry power; if underdifferentiated, slide can be carried back into alcohol; if overdifferentiated, it is practically useless. Decolorizing in acid-alcohol and restaining are possible but results do not justify the effort; better cut new sections.

Moderate amount of leeway is permissible in the timing noted above. The schedule used in our laboratory is usually as follows:

First Day. 9 A.M.: operation, fixation of tissue; 1 P.M.: washing begins; 5 P.M.: decalcifying fluid.

Second Day. 9 A.M.: washing begins; 1 P.M.: 95 per cent alcohol.

Third Day. 9 A.M.: absolute alcohol; 2 P.M.: chloroform; 2.45 P.M.: paraffin, 40 to 42° C.; 3.45 P.M.: paraffin, 53° to 56° C.; 4.45 P.M.: embed.

This procedure can be shortened but sections are not so perfect if tissue is rushed.

Methods for Examination. I. SECTION. A general estimate of the percentage of marrow cellularity should be made with the low-power objective and compared with the approximate normal at the given age (see chart in previous article⁴), to determine hyperplasia or hypoplasia. Using the oil-immersion objective, a differential count should be performed. This is simplified by the use of a ruled ocular (Zeiss-Okularnetzmikrom) to divide the field into segments. At least 90 to 95 per cent of all cells are identifiable in a well-made preparation, according to our experience. The cells should be listed as follows:

Granulocyte Series (Neutrophil, Eosinophil, Basophil):

- Myeloblasts
- Promyelocytes
- Myelocytes
- Metamyelocytes
- Juvenile forms
- Stab forms
- Segmented forms

Erythrocyte Series:

- Megaloblasts
- Early erythroblasts
- Intermediate (polychromatic) erythroblasts
- Late erythroblasts
- Normoblasts

Megakaryocyte Series:

- Megakaryoblasts (mononuclear)
- Megakaryocytes
- Degenerating forms

Cells of the Reticuloendothelial System:

- Reticular forms
- Endothelial forms
- Wandering forms
- Primordial cells (corresponding to so-called hemohistioblasts, hemocyto blasts, lymphoidocytes, etc.)
- Lymphocytes and plasma cells

Attention is also given the following: 1. The general arrangement of the hemopoietic pattern.

2. The activity of one or another of the cell series, as indicated by increase in numbers of immature forms and mitotic figures.

3. A hypoplasia of any or all of the cell series.

4. A defect in development of a series (maturation arrest) indicated by the degeneration or absence of maturing and mature forms.

5. The presence of focal necroses with special note of the type of cell response in the periphery of such necroses, and the presence or absence of bacteria in the necrotic center.

6. The proliferation and phagocytic activity of cells of the reticuloendothelial system, or their tendency to differentiate toward one or another cell type.

7. The replacement of hemopoietic tissue by cells foreign to the bone marrow (lymphocytes, plasma cells, tumor cells, etc.).

8. Evidence of gelatinous degeneration (distinguished from edema¹²) or of osteitis fibrosa.

II. SMEAR. The value of the marrow film lies in the comparison of obscure cell types found in the peripheral blood with cells of the marrow, staining technique being alike. A differential count should be performed in a manner similar to that used with the blood film. Bacterial stains may be applied to the smear with much more ease than to sections and should be done in all cases; care must be exerted, however, to use freshly cleaned slides and to make the smears before there is chance of contamination of the material. At this point it might be well to mention the value of bacterial culture; this must be done at the operating table.

III. SUPRAVITALLY STAINED PREPARATIONS. It is not within the scope of this paper to discuss in detail the staining properties and means of identification of cells stained by this method. The same principles are applied to cells of the blood-forming organs as to those of the circulating blood. Reference is made to the articles of Doan, of Forkner, of Hall and of Tompkins.

IV. CULTURE. This procedure may be of some value when cells of the circulating blood are so undifferentiated that their positive identification on morphologic grounds is impossible. At least 12 cultures should be prepared and placed in the incubator, immediately after the tissue is removed; in addition to frequent observation under the warm-stage microscope, a culture should be fixed at convenient intervals of from 6 to 12 hours and stained by the method used on the blood films.

Dangers of Biopsy. The dangers are those attendant upon any surgical procedure, chiefly the possibility of introducing infection into the myeloid cavity. The author has not encountered a report of ill-effect of this procedure and in his own cases he has never had any reason to regret the biopsy. Tuschinsky and Kotlarenko report 57 sternal punctures without discomfort to the patients. In the

author's series of trephines the incision in all has healed by first intention; the several that have been examined at necropsy have shown no inflammation at the site of biopsy. Patients have not complained of pain during the operation, nor of discomfort other than slight "soreness" thereafter.

Limitations of Biopsy. The clinician who anticipates from the pathologist a definite diagnosis in every case upon which biopsy is performed is doomed to many disappointments—such is often impossible. The diseases that present a specific marrow picture upon which a definite diagnosis can be based are comparatively few. Although the marrow picture may not be specific *per se*, an intelligent correlation of the clinical and peripheral blood features greatly widen the possibilities of the procedure.

Value of Biopsy. Disease of the hemopoietic system can occur without demonstrable change in the blood picture; others may present in some phases of their course an extremely puzzling clinical and hematological syndrome; these are the type cases that show sufficient alteration in the blood-forming organs that a definite diagnosis is made possible by bone marrow biopsy. Again, many diseases, not primarily related to the hemopoietic apparatus, produce changes in the blood picture that are deceptive (reference is made especially to the differentiation between leukemoid reactions and leukemia, between secondary granulocytopenia and the disease agranulocytosis [Figs. 1 to 4], between the various types of pseudo-pernicious anemia and true pernicious anemia, etc.), thus altering the prognosis in many cases.

Aside from the diagnostic features, the course of a given disease can be followed by repeated biopsy; new light may be thrown on the nature of the diseases of the hemopoietic system through study of the bone marrow *in vivo*.

Summary. A method for biopsy of bone marrow and for examination of material removed thereby is presented. The dangers, limitations and value of the procedure are mentioned.

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LEUKEMIAS SHOWING HAPLOID LEUKOBLASTS UNDERGOING MITOTIC DIVISION IN CIRCULATING BLOOD.

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THE various types of leukemia are blood-stream expressions of a disease involving the hematopoietic system in whole or in part.¹ The leukemic blood picture is a fluid metastasis.² The abnormal cells found in the blood in a leukemia also are found more or less throughout the hematopoietic system. A so-called "aleukemic" period probably precedes the appearance of a leukemic blood picture. Such infiltrations as may be found in various organs and tissues are made up of the type cell of that particular case. Each

case of leukemia has individuality, a more or less characteristic cell classifies it, and this characteristic cell and the individuality point to abnormality. For example, in a myeloid leukemia, one finds that the abnormal myeloblastic type of cell, which characterizes it and is commonly used to name and classify it, is one which resembles a cell type normally found somewhere along the differentiation chain between the most primitive myeloblast and the myelocyte. There are myeloid leukemias in which the proliferating abnormal cell is so primitive as scarcely to be recognizable, perhaps to be called merely a stem cell; and other cases may be characterized by cells resembling normal types up to the myelocyte, but none beyond the myelocyte. There are no preleukocytic or polymorphonuclear leukocytic leukemias. There are no leukemias beyond the stage of differentiation when mitosis ceases (the myelocyte) and differentiation continues by aging only.

Histologic study of normal marrow shows mitotic division going on from the primitive stem cell through the phases of differentiation up to and including the young myelocyte. This end point of mitotic division is also the normal dividing line between marrow and circulating blood. In a leukemia state active mitotic division often is found in the abnormal cell which characterizes it in sections of marrow and involved fixed tissue. I have reported³ a case of acute myeloblastic leukemia in which all phases of mitotic division in the characteristic cell of that particular case were found in the peripheral blood. Bowcock and Bishop⁴ reported a case in which they found mitotic figures in peripheral blood and thought that many of them were in leukoblasts. I have had the privilege of studying the original smears and agree with them that most of the cells, as illustrated in their paper, are leukoblasts undergoing mitotic division. Bowcock with Dickson has reported a second case,⁵ smears from which also I have studied and photomicrographed. Rabinovici⁶ reported a case which, while not illustrated, by description undoubtedly belongs in this group. The first paper which comprehensively approaches this topic is that of Dock.⁷ He collected cases of leukemia in which mitotic figures had been reported found in the peripheral blood. Some of these reports undoubtedly referred to erythroblasts, others probably to leukoblasts, and in his own illustrated cases some are erythroblastic and others indubitably leukoblastic, although he did not definitely separate them.

Directly after the appearance of my report, Dr. Raphael Isaacs, in a personal communication, called my attention to the fact that the cells illustrated by me were haploids; that is, contained half the full somatic number of chromosomes to be expected in human blood cells (48) and directed me to a discussion by him⁸ in which he stated he had found similar cells in a leukemia. In this discussion he ventured the suggestion that the haploidal character of the cells might explain their abnormalities and seeming inability

further to differentiate into more mature types. He tells me his case is soon to be reported.

I present 6 additional cases, and so far as can be determined, in all of these the cells in mitotic division are haploids. Well over 200 leukemic cells undergoing mitotic division, from 12 different cases, have been studied and photomicrographed. In those in which the chromosomes could be estimated or actually counted, the number was found to be usually 24, or of the order of 24 rather than 48, indicating them to be haploids. A few with irregular chromosome numbers were found, as might be expected, but in none did I find what appeared to me to be the full somatic ($2n$) number of chromosomes. From Dr. Wiseman's case, in which mitotic figures were found by me, and the illustrations used herewith through Dr. Wiseman's kindness, myeloid cells undergoing mitotic division are shown in complete series from prophase to telephase. (Plate I.) In the 12 cases studied, the mitosis is found in the type cell characteristic of the case. The captions for the selected illustrations on Plates I and II I believe are sufficiently clarifying and attention is directed to them.

Discussion. In my former paper³ I drew the following as one of the conclusions: "Mitotic division in leukemia cells in peripheral blood is added evidence of possible relationship between leukemia and malignancy." From the literature and these illustrated cases, it seems likely that in the leukemic states there is often active irregular mitosis in the type cell in the peripheral blood as well as in the marrow, lymph nodes, spleen and tissue infiltrations. The similarity to the malignancies is further emphasized. We have in the leukemic states an abnormal cell which typifies the case, which proliferates without differentiating, in which active mitosis is found, the active mitosis being found also in the fluid metastasis in the blood stream when that picture is present. It has long been recognized that leukemic cells are abnormal and immature. The degree of apparent maturity varies as in the malignancies. The resemblance of the abnormal cell types to the normal prototypes varies as in the malignancies, and in each is sometimes difficult to recognize. In both the cells are often imperfect and bizarre.

The leukemias have been grouped apart from the sarcomata largely because of the definite tendency for the abnormal growth to cling to the hematopoietic system, perhaps only infiltrating here and there; but one finds in the leukemic states, such as the chloromas, certain types of sarcomatous lymphoblastomas and myeloblastomas, both the invasive tumor and the leukemic blood picture. One of the cases shown herewith is definitely of that type. James⁹ reports such a case in which mitotic figures were found in the peripheral blood. Through Dr. James' kindness, I have had the privilege of studying and photographing the films of this case also.

Blood cells are highly specialized. Early in embryonic life they are differentiated in the mesoderm. It is essential that one of their early and firmly fixed characteristics should be that they stay within, or normally find comfortable environment only within, the hematopoietic system, at least until maturity. One may perhaps conclude that when abnormal and immature and invading the blood stream before their time has come they should rarely find a suitable environment outside the system itself, and therefore rarely succeed in other tissue to the extent of actual invasive tumor formation. Instead of this being a differentiation from the malignant tumors generally, it is a similarity more striking because of the highly differentiated character of blood cells in a closed system. All tumors at first are local, seem to spread more rapidly and easily in their own type of tissue, and, when they do metastasize, often have certain tissues into which they most readily choose to go. Sarcomas with hematopoietic system and blood stream metastases and leukemias with general tissue metastases of invasive nature seem closely related and for somewhat similar reasons are equally rare.

The fact that at least some leukemia cells are haploids may be of considerable importance from a biologic and a pathologic standpoint. In a general consideration of the possibilities one should keep in mind the fact that by mitotic division living matter is perpetuated and characteristics are transmitted from generation to generation. The nucleus of the typical cell is its center of control for growth and development. A resting nucleus has definite structure with a limiting membrane and shows a network of chromatin. The chromatin granules which make up this nuclear network seem to be the instruments for transmission of specific qualities or characteristics from cell to cell and, in the higher forms, from parent to offspring. In the cytoplasm of a typical cell resting near the nucleus is a small body called the *centrosome*. This organ seems to be the controlling factor for mitotic division of the cell. The first recognizable step in mitosis is division of the centrosome into two parts. These daughter centrosomes separate and show a radiating halo of fine lines and as they move to opposite sides of the nucleus the radiating lines between them are prolonged, forming a bundle of delicate fibers like lines of force. This bundle is called the *spindle*. Directly after the division of the centrosome the nucleus begins to show changes, the chromatin network becomes coarser and more definitely separate and its granules gradually are arranged in a continuous thread, typically a tangled skein, called the *spireme*. This thread soon breaks up crosswise into a number of segments, usually an even number, called *chromosomes*, and the number of these segments is constant for all somatic cells of a given species. By this time the nuclear membrane has disappeared.

The chromosomes now separate and are drawn to the center of the spindle and arranged in a plane at right angles to the spindle midway between the two centrosomes to form what is called the *equatorial plate*. This marks the end of that preliminary stage of mitosis called the *prophase*. Now each chromosome separates into 2 parts, splitting longitudinally in such a manner as to give an even division of chromatin, forming two sets of chromosomes parallel to one another along the equatorial plate. This is the *metaphase*. The two sets of daughter chromosomes now start to move in opposite direction along the spindle to the poles and then arrange themselves around each daughter centrosome so that each centrosome becomes the possessor of a full set of daughter chromosomes, the same number as in the mother cell. This period of shifting is called the *anaphase*. The last stage, *telophase*, now follows, featuring reconstruction of the 2 daughter groups of chromosomes into resting nuclei, chromosomes becoming indistinct with granules scattering to rebuild chromatin networks, and new nuclear membranes form. Meanwhile the cytoplasm becomes grooved at the region of the equatorial plate, and it finally cleaves, forming 2 finished daughter cells.

Chromosomes carry the *genes* which determine the characteristics of the individual and transmit the characteristics from cell to cell and from generation to generation by mitosis. If a chromosome is damaged or experimentally removed, definite characteristics are lost. The fertilized ovum, however, and every cell descended from it, has a double set of chromosomes, 1 set from each parent, and, therefore, all cells of the soma are called *diploids*. A haploid is a cell containing half the full somatic number. There are normal haploids. In spermatogenesis and oögenesis, by somewhat different but essentially similar processes, the number of chromosomes in the sperm and ovum is reduced one-half to the haploid number. A fertilized ovum has received 1 haploid group of chromosomes from each parent through union of sperm and ovum, and transmits this double number to the cells of the entire body structure by mitotic division. Certain plants, the mosses and ferns, have alternate generations which differ markedly in function and appearance. The members of 1 generation are comparatively large, conspicuous plants whose cells are diploid. Those of the alternate generation arising from the germination of spores from the preceding one are tiny and inconspicuous, but possess reproductive organs capable of forming the equivalent of sperm and ovum for procreation of the commonly recognized form again in the next generation. The individuals of this inconspicuous generation are haploids.

Haploidal cells do occur accidentally and usually have a complete half set of chromosomes. They are easily injured, their vitality seems impaired and their lives are short. Normal haploids possessing a full half set of chromosomes must not be confused with cells



PLATE I.—(FROM ORIGINAL PHOTOMICROGRAPHS. $\times 1200$.)

Selected series of mitotic figures in progressive stages, prophase to telophase, in promyelocytes from blood; chronic myeloid (promyelocytic) leukemia. (Dr. Wiseman's case.)



PLATE II.—(FROM ORIGINAL PHOTOMICROGRAPHS. $\times 1200$.)

FIGS. 1 and 2.—From a very chronic myelocytic leukemia, showing mitotic myelocytes.

FIGS. 3 and 4.—From a chronic myelocytic leukemia, showing mitotic myelocytes.

FIG. 5.—From an acute myeloblastic leukemia with invasive myeloblastomata, with mitotic cells of same type in blood and tumor.

FIG. 6.—From an acute myeloblastic leukemia, showing mitotic myeloblasts.

FIGS. 7 and 8.—From a chronic promyelocytic leukemia with mitotic promyelocytes.

in which half of the number of individual chromosomes may have been destroyed in their entirety. When a whole chromosome is destroyed important characteristics are lost. Defectives and monsters result. If certain chromosomes from sperm (or unfertilized ovum) are damaged or destroyed, breaking the pair in the fertilized ovum, weaknesses and defects develop.

In cases of leukemia in which haploidal leukoblastic cells are found it would be of great interest to know where the reduction in the number of chromosomes took place, why it took place and how the reduction was accomplished.

Summary and Conclusion. 1. Six additional cases of leukemia with leukoblasts undergoing mitosis in circulating blood are presented.

2. It is notable that in each instance the mitotic division is going on in the typical cell characterizing the particular case. If the case is a highly primitive myeloblastic leukemia, mitosis is in the highly primitive myeloblastic cell;³ if it is a promyelocytic type of myeloid leukemia it is in the promyelocyte; and if myelocytic it is in the young myelocyte.

3. Attention is directed to the fact that leukemias and leukemic states can arise only from cells within the differentiation periods in which division by mitosis is normally found. We do not have leukemias beyond that point; that is, beyond the young myelocyte, after which differentiation takes place by aging.

4. The important finding of Isaacs that cells undergoing mitotic division in a human leukemia were haploids is further amplified by additional cases, no leukoblastic mitotic figures being found in cases studied which had the full somatic number of chromosomes.

5. Many similarities between the leukemic states and malignancies are shown and some of the supposed differences in a way accounted for.

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THE SYNTHESIS OF HIPPURIC ACID: A NEW TEST OF LIVER FUNCTION.*†

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ONE of the important functions of the liver is the detoxication of noxious substances that are either ingested or arise in the gastrointestinal tract. Of the detoxication processes, the conjugation mechanisms are of particular interest because not only does the organism apply these to a wide variety of substances, but also because these mechanisms seem to be definitely interrelated with various normal physiologic functions. Thus, the writer¹ has recently found that many aromatic acids, such as benzoic acid and phenylacetic acid, will produce a marked decrease in the excretion of uric acid, and the duration of this inhibiting effect coincides with the time required by the organism to conjugate and eliminate the particular drug. Thus, since any impairment of a detoxication mechanism is apt to bring about a disturbance in normal physiologic processes, the importance of determining the efficiency of the conjugation mechanisms becomes apparent.

The conjugation of benzoic acid with glycine to form hippuric acid is undoubtedly the best known and the most thoroughly studied of all the detoxication mechanisms; nevertheless, it has received comparatively little attention in clinical medicine. The reason for this can probably be found in the fact that, due to the discovery of Bunge and Schmiedeberg² that in the dog hippuric acid is synthesized only in the kidney, almost all subsequent workers tacitly assumed that in man likewise the formation of hippuric acid depended primarily on the kidney. This resulted in various efforts to utilize the conjugation of benzoic acid as a test of kidney function. Bryan³ is the only investigator who has studied the synthesis of hippuric acid in human subjects with hepatic involvement. Unfortunately the analytical methods available to Bryan were tedious and somewhat unsatisfactory; nevertheless, his results definitely indicated that liver damage did influence the conjugation of benzoic acid.

* This work was aided by a gift of Mrs. John L. Given in support of surgical research.

† A preliminary note of this work was published (Proc. Soc. Exp. Biol. and Med., 1932, 29, 1204).

It is quite probable that in man, as in the rabbit,^{4,5} the synthesis of hippuric acid also takes place in the liver. Furthermore, the writer⁶ has demonstrated that the rate of the synthesis of hippuric acid is dependent upon the speed with which the organism furnishes glycine. Irrespective of the amount of benzoic acid administered, the quantity of hippuric acid excreted per hour (in the absence of exogenous glycine) is relatively constant, indicating a definite maximum capacity of the organism to synthesize glycine. Since it is commonly accepted that glycine is formed in the liver, it seemed probable that certain types of liver damage might produce impairment of this synthesis, which should result in a diminished output of hippuric acid. On this basis a new test of liver function was developed.

The Test. Five and nine-tenths grams of sodium benzoate dissolved in 30 cc. of water is administered 1 hour after a breakfast consisting of coffee and toast. The patient is then given $\frac{1}{2}$ glass of water. Immediately after taking the drug the patient voids, and then collects complete hourly specimens for 4 hours. These are preserved with toluene, and hippuric acid determined in each specimen. In normal adults the output of benzoic acid as hippuric acid is approximately 1 gm. or more during the second and third hours, and the total for the 4 hours is from 3 to 3.5 gm.

For clinical purposes a simple method has been developed which will be described as Method 1. If greater accuracy is desired the formol method previously described by the author⁷ is recommended. In the present work, hippuric acid was determined by both methods, and the results obtained by the simpler clinical method agreed satisfactorily with the formol titration method. No substances have been encountered which interfere with either method.

Method 1. Simpler Clinical Method. Each hour specimen is measured, transferred to a small beaker and acidified with concentrated hydrochloric acid until acid to Congo red; 1 cc. of the acid is usually sufficient. The solution is vigorously stirred until the precipitation of the hippuric acid is complete, and then is allowed to stand for 1 hour at room temperature. The precipitate is filtered off on a small Buchner funnel or a filter plate, washed with a small quantity of cold water and allowed to air dry. The hippuric acid thus obtained is either weighed (to the second decimal place, which is sufficiently accurate) or titrated with 0.2 N sodium hydroxide, using phenolphthalein as indicator. To obtain the total hippuric acid, one must add to the amount thus obtained the calculated quantity remaining in solution; 100 cc. of urine will dissolve 0.33 gm. of hippuric acid. In case any specimen exceeds 125 cc. it should be slightly acidified with acetic acid and concentrated on the water bath to about 50 cc. before precipitating the hippuric acid. The results are best expressed in terms of benzoic acid. To convert hippuric acid to benzoic acid, one multiplies by 0.68.

Method 2. This determination depends on the isolation of hippuric acid from the urine by extraction with ether, and subsequent hydrolysis by means of hydrochloric acid. The glycine thus liberated is determined by the well-known formol titration: 5 to 10 cc. of urine are transferred to the extraction tube of a continuous extractor,* 1 cc. of 5 N sulphuric acid and 2 drops of 10 per cent sodium tungstate added. The sample is extracted with ether for 90 minutes. The ether is removed by distillation, 10 cc.

* The extractor used is described Industrial and Engineering Chem., Anal. Ed. 1933, 5, 76.

of 20 per cent hydrochloric acid is added to the crystallin residue, and the flask is connected with an air condenser. The solution is refluxed on a hot plate for 1 hour, and then is transferred to a small dish, and evaporated to dryness on a water bath. The residue is dissolved in about 20 cc. of hot water, a small amount of decolorizing charcoal (norit) added, and the solution filtered. The residue is washed several times with hot water. One drop of 1 per cent neutral red indicator is added to the filtrate, which is then neutralized to pH 7. At this pH neutral red is slightly pink, *i. e.*, midway between yellow and red. Six drops of 1 per cent phenolphthalein and 10 cc. of neutralized 40 per cent formaldehyd are added, and the solution titrated with 0.1 N sodium hydroxid until the deep red color matches the standard, which is prepared by mixing 20 cc. of distilled water, 10 cc. of neutralized formaldehyd, 6 drops of phenolphthalein, 1 drop of neutral red and 0.3 cc. of 0.1 N sodium hydroxid. Since 1 cc. of 0.1 N sodium hydroxid is equivalent to 1 cc. of 1 N glycine, the titration value, corrected for the 0.3 cc. blank, can be converted directly either to hippuric or benzoic acid.

Discussion. From the results obtained in the present study it can be definitely concluded that the synthesis of hippuric acid is strikingly diminished in several types of liver diseases. In the series of cases investigated, catarrhal jaundice and luetic cirrhosis gave consistently low results, cholecystitis without jaundice showed a normal output, while obstructive jaundice gave somewhat less consistent results. Two cases giving a history of common duct stone with spontaneous recovery yielded normal results, but patients with a progressively deepening jaundice in which the etiologic factor was usually a neoplasm gave low results, and in 1 extreme case (Case 7) an excretion of only 0.56 gm. of benzoic acid in 4 hours was obtained. Two cases of nonluetic cirrhosis gave normal results. A diminished output of hippuric acid was found in a number of patients with an enlarged liver in which the diagnosis was doubtful. One case of pernicious anemia with an enlarged liver showed a decided impairment, and another patient with a large tender liver and an incidental alkaptonuria likewise gave a low output. It should be noted that a marked increase in the excretion of hippuric acid was obtained by feeding glycine to those cases showing impairment of the conjugating mechanism.

Bryan,³ who in his study of sodium benzoate as a test of kidney function included a small series of cases with hepatic involvement, recorded a definite reduction in the excretion of hippuric acid in several of these patients, but he apparently failed to appreciate the significance of his results. One of his patients with toxic jaundice following arsphenamin gave distinctly low results. It is highly probable that this type of case will consistently have a low output. In 2 cases of toxic jaundice, not recorded in the table, a diminished excretion of hippuric acid was noted, but as vomiting occurred, it was difficult to determine how much sodium benzoate had been retained.

Vomiting is one of the difficulties encountered when the test is applied to toxic patients. In other patients it occurs only rarely

and it is greatly minimized by allowing a light breakfast prior to the test. In sensitive patients it is probably best to employ a smaller dose of sodium benzoate. The other disadvantage of the test is that it cannot be applied to cases of nephritis with nitrogen retention, since hippuric acid behaves like other nitrogenous excretory products. Fortunately this complication is not frequently encountered in the ordinary liver cases.

From the data in Table 1 one is led to conclude that the new test not only discloses liver impairment, but actually promises to furnish an approximate quantitative measure of the amount of damage sustained. In defense of this test, an adequate answer can be given to the two stereotyped objections that are levied against every liver test, namely, that the reserve power of the liver is so great that impairment of function can only be demonstrated after extensive damage has occurred, and that the functions of the liver are so numerous that a test of any one of them fails to give reliable information concerning the state of the organ as a whole. While the reserve of the liver as measured by the amount of the organ that can be removed surgically without causing death is very great, it must not be forgotten that certain mechanisms of the liver are so delicate that there is practically no margin of safety. Smyth and Whipple⁸ found that a dose of chloroform, so small that no morphologic changes of the liver epithelium were produced, nevertheless caused a distinct reduction in the excretion of bile acids. The writer likewise has found that in dogs a light chloroform anesthesia will result in a marked diminution in the output of glycuronic acid. The test itself demonstrates that the mechanism concerned with the synthesis of glycine has little reserve, for the marked reduction in the excretion of hippuric acid in catarrhal jaundice is out of all proportion to the amount of structural change observed in this disease.

While the test measures only one mechanism of the liver, it must be realized that the various functions of this organ are not distinct and independent, but are closely interrelated, so that an injury to any one mechanism is apt to affect several others as well. Many examples of this interlocking of functions can be cited. Thus, the synthesis of amino acids such as glycine, on the one hand, depends on a precursor which is presumably derived from the metabolism of carbohydrates, while the formation of bile acids, on the other hand, requires an ample supply of glycine and taurine. Furthermore, it is quite probable that the so-called detoxication mechanisms are in reality mainly concerned with normal metabolic processes, and the conjugation of abnormal substances is only an incidental function. For example, the mechanism that synthesizes glycocholic acid, *i. e.*, brings about the conjugation of cholic acid with glycine, is probably the same which effects the union of benzoic acid with glycine. It is significant that obstructive jaundice, which brings about a decrease in the formation of bile acids, as has been noted

by Greene, Walters and Fredrickson,⁹ Ravdin¹⁰ and others, also causes a reduction in the output of hippuric acid. As a further parallelism, the production of bile acids and of hippuric acid does

TABLE 1.—THE EXCRETION OF HIPPURIC ACID IN CASES OF HEPATIC INVOLVEMENT.

Case.	Age.	Enlargement of liver.	Jaundice.	Van den Bergh direct.	Nonprotein nitrogen, mg.	Excretion of hippuric acid in terms of benzoic acid.					Diagnosis and summary.
						1 hr., gm.	2 hrs., gm.	3 hrs., gm.	4 hrs., gm.	Total, gm.	
1	36	0	0	0.55	0.76	0.84	0.84	2.99	Normal weight, 52 kg.
2	55	0	0	0.55	0.96	1.03	1.01	3.55	Normal weight, 58 kg.
3	29	0	0	0.85	1.11	0.63	0.61	3.20	Normal weight, 78 kg.
4	42	+	0	..	38	0.21	0.54	0.40	0.32	1.47	Luetic cirrhosis; marked secondary anemia.
5	46	+	9*	Delay.	36	0.31	0.33	0.47	0.40	1.51	Luetic cirrhosis.
6	51	+	0	0.11	0.28	0.39	0.31	1.09	Luetic cirrhosis with ascites.
7	68	Sl.	90	Imme.	34	0.18	0.70	0.51	0.44	2.13	3 gm. glycine given.
8	44	+	100	Imme.	0.68	0.65	0.50	1.83	Carcinoma of head of pancreas (clinical).
9	60	+	+	0.24	0.55	0.73	0.80	2.32	Carcinoma with metastasis to liver.
10	55	+	6	0.48	0.60	0.64	0.69	2.41	Carcinoma with metastasis to liver.
11	40	+	+	0.48	0.60	0.37	0.75	2.20	Bronzing of skin; mass in mediastinum.
12	51	+	0	..	38	0.22	1.26	0.84	0.52	2.84	Tumor of liver close to common duct; laparotomy 2 yrs. ago.
13	49	0	0	0.37	1.46	0.54	0.61	2.98	Hypertrophic cirrhosis (clinical); mass in U.L.Q.
14	41	Sl.	70	Imme.	35	0.29	1.07	0.95	0.94	3.25	Atrophic cirrhosis with ascites (autopsy).
15	39	0	50	..	34	0.46	0.97	1.09	0.44	2.96	Common duct stone; spontaneous recovery.
16	55	Sl.	+	Imme.	..	0.37	0.63	0.63	0.55	2.15	Common duct stone; spontaneous recovery.
17	37	Sl.	65	0.30	0.37	0.38	0.49	1.44	Cholecystitis and cholelithiasis.
18	42	0	3	0.47	0.43	0.45	0.17	1.52	10 days later; jaundice completely cleared up.
19	45	0	0	0.71	1.01	0.88	0.56	3.16	Stricture of common duct.
20	40	0	0	0.84	0.79	1.20	0.60	3.43	Cholecystitis (subacute).
21	42	0	0	0.48	1.01	1.60	0.50	3.59	Cholecystectomy 1 yr.
22	40	0	0	0.85	0.70	0.67	0.53	2.75	Cholecystitis (chronic).
23	38	0	0	0.51	1.48	0.98	0.16	3.13	Cholecystectomy 6 mos.
24	33	0	75	Imme.	32	0.38	0.99	1.17	0.72	3.26	Cholecystectomy 5 mos.
25	29	0	80	Imme.	..	0.21	0.17	0.67	0.75	2.10	Cholecystectomy 1 mo.
26	25	0	70	Imme.	..	0.16	0.35	0.44	0.37	1.32	Catarrhal jaundice.
27	27	0	+	0.48	0.60	0.63	0.57	2.28	Catarrhal jaundice.
28	56	+	75	Imme.	..	0.24	0.35	0.30	0.47	1.36	2 days later; 2 gm. glycine given.
29	44	+	0	0.47	0.65	0.36	0.90	2.35	14 days later.
30	38	+	0	..	30	0.67	1.34	0.95	0.18	3.10	Catarrhal jaundice.
31	..	0	0	0.48	0.45	0.46	0.75	2.14	2 days later; 3 gm. glycine given.
32	36	0	0	0.27	0.57	0.84	0.42	2.10	4 days later.
33	55	0	0	0.65	0.99	0.98	0.59	3.21	Catarrhal jaundice.
34	51	+	0	0.35	1.12	1.18	0.34	2.99	Complete clinical recovery, 1 mo. later.
35	61	0	0	0.11	1.32	1.43	Cholelithiasis.
36	..	0	0	0.11	0.50	0.62	0.43	1.66	6 days later.
37	..	0	0	0.33	0.43	0.55	0.53	1.84	Sudden onset of U.R.Q. tenderness and fever; alkapturia.
38	..	0	0	0.39	1.14	0.91	0.58	3.05	Pernicious anemia.
39	..	0	0	0.30	0.80	0.63	1.63	3.36	3 days later; 3 gm. glycine given.
40	..	0	0	1.15	0.90	1.35	0.21	3.61	Pernicious anemia.
41	..	0	0	0.65	0.84	0.66	0.78	2.93	Mild hepatitis following arsenphenamin.
42	..	0	0	0.29	1.32	0.86	0.54	3.01	Luetic arthritis.
43	..	0	0	0.89	1.32	0.56	0.19	2.96	Hypertension; mass in U.Q.
44	..	0	0	0.65	0.84	1.05	0.85	3.39	Alcoholic neuritis.
45	..	0	0	Myasthenia gravis.

* Icterus index.

not immediately return to normal after the relief from the obstruction but is definitely delayed. Case 16, in fact, showed a distinctly lower output of hippuric acid after the jaundice had disappeared. The relief of biliary stasis does not necessarily mean an immediate restoration of the liver to the normal state, but with the exception of the hippuric acid test there is no simple method for determining when complete recovery has taken place. The usefulness of the test is illustrated by Case 27. The first test was performed at the time when the patient had practically recovered; nevertheless, she showed a definitely diminished excretion of hippuric acid. A month later, however, she was entirely normal.

Since the synthesis of hippuric acid constitutes a measure of a protective mechanism of the body, the test should become useful to the surgeon in his choice of anesthesia, in his pre-operative care and his preparedness for emergencies. For the internist it should prove equally valuable, since a diminished excretion of hippuric acid should be a contraindication for arsphenamin, einchophen, neo-einchophen and other drugs having potential hepatotoxic properties.

While the results thus far obtained are suggestive of the usefulness of the test as an aid in the diagnosis of hepatic diseases, a comprehensive estimate of its scope can only be made after a larger series of cases has been studied and a correlation with other tests and autopsy findings has been made. The fact that luetic cirrhosis shows such a distinct diminution in the synthesis of hippuric acid makes it seem probable that the test may become useful in detecting early syphilis of the liver, as well as the dormant type which is now rarely detected.

Summary. A simple test for liver function, depending on the excretion of hippuric acid following the administration of sodium benzoate, is described.

Diminished excretion of hippuric acid was observed in luetic cirrhosis, catarrhal jaundice and in obstructive jaundice of moderately long standing. Normal results were obtained in cholecystitis and in 2 cases of portal cirrhosis.

The results obtained indicate that the test offers an approximate quantitative measure of liver damage, and a valuable aid in the diagnosis of liver diseases.

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THE RÔLE OF THE LIVER IN THE TOLERANCE OF THE DOG TO QUINIDIN.

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THIS study was prompted by the observation that small doses of quinidin sulphate administered to a patient with early unrecognized portal cirrhosis produced marked toxic symptoms, and that with continuation of the drug acute yellow atrophy of the liver developed. We have not found in the literature any report of a similar case, but have since encountered another where small doses of quinidin produced toxic effects. While we recognize that these events may have been coincidental, nevertheless, there is some experimental evidence to suggest that the liver may be an important factor in the destruction of quinin and quinidin, and may, therefore, play a vital rôle in determining the tolerance of the body to these drugs.

Most of the published work on this problem has been done on quinin. Plehn,¹⁴ in 1907, found that 55 per cent to 77 per cent of quinin perfused through the isolated cat's liver in the perfusing fluid was destroyed. Boecker,² in 1923, found that quinin intravenously administered rapidly left the blood stream and was disseminated to all tissues and organs, and concluded, partly on the basis of Plehn's work, that the liver continually destroyed the alkaloid and that the kidney continually excreted it. Since the lethal dose of quinin when injected into the portal vein was found to be 2.6 times as great as when given into a peripheral vein, Roger¹⁶ concluded that the liver destroyed or detoxified the alkaloid. Hatcher and Weiss,⁷ repeating the work of Plehn,¹⁴ obtained similar results. They performed 2 perfusion experiments with quinidin sulphate and found a destruction of 22 per cent and 31 per cent respectively.²³ These 2 experiments constitute, so far as we are aware, the only investigation of the relation of the liver to the destruction of quinidin.

The experimental studies cited, together with our clinical observations, suggested that the rôle of the liver in the body's tolerance to quinidin might be further investigated experimentally. We have endeavored to investigate this question in dogs by studying: 1. in the intact animal: (1) The tolerance to quinidin before and after liver injury; (2) the tolerance to quinidin before and after Eck fistula and exclusion of the liver from the circulation; and (3) by

comparison of the effects of quinidin injected through the femoral vein and portal vein, and femoral vein and femoral artery; and, *B.* in perfusion experiments, the comparative rate of disappearance of quinidin from the circulation in heart-lung, heart-lung-liver, and heart-lung-hind-leg preparation.

A. Studies on Intact Animals. Method. In all our experiments on intact animals, dogs were preliminarily standardized by determining their response to a known amount of quinidin. After complete recovery, they were submitted to one of the procedures indicated above, and their response to quinidin redetermined. We have used two criteria for judging the tolerance of the animal to quinidin: (1) Electrocardiographic findings, consisting of changes in the heart rate and *P-R* intervals, and (2) the chemical determination of the quinidin concentration in the blood.

During all injection studies the animals were completely anesthetized. Under both ether and morphin, vagal effects somewhat interfered with the electrocardiographic results. Sodium amytal (sodium iso-amyl ethyl barbiturate), however, was found to be entirely satisfactory, producing an even anesthesia without interfering vagal effects, and was therefore used in all our experiments.

We found that the continuous injection of small amounts of quinidin, rather than the use of a single large dose, afforded a better opportunity to gauge effects and also resulted in a lower mortality. Therefore, in all our experiments on intact animals, the quinidin was administered intravenously at the rate of 1 mg. per kilo of body weight per minute. The quinidin was dissolved in normal saline solution in such amounts that the total fluid introduced into the circulation was definitely less (usually by more than one-half) than the amount of blood removed for chemical analysis. In practically all our standardizations, where the drug was introduced into the femoral vein, the injections were continued for about 30 minutes, a duration that experience showed led to definite effects but did not bring about dangerously toxic reactions. During and after the period of injection, electrocardiograms were obtained at frequent intervals and at some period of the experiment, usually at the end of the injection, at least one sample of blood was taken for chemical analysis. The method of determining the amount of quinidin in the blood was that of Weiss and Hatcher.¹⁸

Discussion. Several factors which apply to the general method will be considered.

Accuracy of the Method of Determining the Quinidin Content of the Blood. *In vitro*, the method of Weiss and Hatcher¹⁸ has been shown to have an error of not more than 10 per cent, the error when present usually being on the low side. We have repeatedly confirmed this observation.

Assumption that Action of Quinidin is Directly Proportional to Body Weight. It was assumed that the amount of quinidin required

to cause a given response was directly proportional to the body weight, because of the variations in weight of individual animals and of the same animal before and after operation. Of 20 standardizations of normal animals, according to the described method, the values for the amount of quinidin extracted from the blood at the end of injection averaged 1.88 mg. per 100 cc., the lowest figure being 0.98 and the highest 2.72 mg. per 100 cc. of blood. In only 6 were the figures more than 25 per cent above or below the average of 1.88 mg. (+29 per cent, +30 per cent, +44 per cent and -28 per cent, -28 per cent and -47 per cent). The individual variations and error of the method are illustrated by the blood concentrations of quinidin obtained from the same animal on 2 different occasions before operation, the weight being the same in both instances. In mg. per 100 cc. of blood the figures were 2.9 and 2.05 mg. per cent, a variation of approximately 30 per cent. Allowing for the error in the determination of quinidin in the recovered blood and the variation in the response of the individual animal, we feel that there is sufficient consistency in these results to warrant our assuming that the calculation of the required amount of quinidin on the basis of the body weight cannot be seriously questioned.

Effects of Alteration in Blood Pressure. Although the intravenous administration of quinidin produced a lowering of blood pressure in the normal animal, we found in a number of studies that there was no greater fall of the pressure after liver damage than before. Lowering of the blood pressure, therefore, could not account for the difference of the blood quinidin figures before and after liver injury.

Fall in blood pressure *per se* we do not believe to have been a factor in influencing the electrocardiographic criteria that we used in judging the effect of quinidin. Studies made in our laboratory by Wood, North, and Ferguson²² showed no slowing in rate or increase of *P-R* intervals of a number of dogs, the blood pressure of which fell greatly during spinal anesthesia and shock.²²

The Electrocardiogram as an Index of Quinidin Action. That quinidin produces definite effects on the electrocardiogram is well known.^{4,10,11,17} The decrease in rate and observed changes in *P-R* intervals when plotted in the form of curves were found to be fairly constant in the animals studied. One typical graph is shown in Fig. 3. The electrocardiographic changes usually ran parallel to the blood concentration of quinidin. Changes in the *P-R* intervals were found to be a more reliable guide than the rate, the former being apparently less susceptible to external influences. A slight difficulty arose in 3 of our jaundiced animals (Dogs 461, 386, and 483) where, probably as a result of the liver damage and the stimulating vagal action of bile salts, the cardiac rate was diminished and the *P-R* intervals slightly increased above the corresponding pre-operative values. However, the increases in the electrocardiographic

effects that followed the introduction of quinidin into these animals were so definite that there was little doubt as to the direction in which they pointed.

A Comparison of the Dog's Tolerance to Quinidin Before and After Liver Injury. The method of damaging the liver in these experiments consisted in greatly increasing the intrahepatic ductal pressure by tying and severing the common bile duct after cholecystectomy.

Procedure. This procedure resulted in a varying degree of liver damage and caused the development of a moderate to a severe jaundice (5 to 30 van den Bergh units). In spite of jaundice and slight loss of weight, dogs subjected to this procedure appeared to be in relatively good condition for a period much longer than the duration of the experiment—in some instances as long as 3 months.

Grossly, the livers thus damaged showed not only passive congestion but a definite patchy green discoloration. Microscopically, the large bile ducts were markedly distended as were the bile capillaries. This was accompanied by bile stasis within the lobule. The liver cells showed definite parenchymatous changes, in the form of fatty degeneration and hydropic vacuolization. In some livers the degeneration was so marked that it extended toward the periphery and definitely beyond the central groove of congestion. The periportal tissue was increased in all cases. In some animals it was compact; in others, it was edematous and accompanied by fibroblastic and angioblastic proliferation, and contained inflammatory exudate. In conjunction with the above fibrosis, all the bile ducts showed some degree of hyperplasia.

The standardization of the dogs before the operation was done by administering intravenously 1 mg. of quinidin sulphate per kilo of body weight per minute in the form of a 1 per cent solution in normal saline. During the injection, electrocardiograms were taken every minute and changes in the rate and *P-R* intervals determined. The introduction of quinidin was continued for from 27 to 30 minutes, at the end of which time 100 cc. of blood were removed from the femoral artery and the concentration of quinidin determined. After at least 1 week, the livers were damaged and then in from 19 to 45 days later, the animals' tolerance to quinidin was re-determined in the same manner.

Results. In all, 7 experiments were performed by the method described (Table 1). In the first 2 experiments, only electrocardiographic studies were obtained. In the remaining 5, chemical as well as electrocardiographic studies before and after liver injury were made. In Dogs 110, 411, and 461, the heart rate after liver injury showed a decrease of from 10 per cent to 25 per cent of that observed at the initial standardization. In Dogs 107, 386, and 483, there was no definite change in the rate, but the *P-R* intervals, which we found to be a more reliable criterion of quinidin effect, showed an increase of from 13 per cent to 100 per cent. Evidence of diminished tolerance was least marked in Dog 107. In this animal, the extrahepatic bile ducts were not completely ligated and the van den Bergh test showed a maximum value of only 2 units. The liver postmortem showed but slight damage, less than in any other animal in the group.

The blood removed from the animals during the standardization after the liver injury showed an increase in concentration of quinidin in the different animals of from 57 per cent to 300 per cent above the preoperative figures. In general, the animals which showed the greatest histologic change in the liver presented the most marked electrocardiographic signs and the highest quinidin recoveries from the blood at the second standardization. In Dog

TABLE 1.—COMPARISON OF EFFECTS OF QUINIDIN INJECTION IN THE NORMAL ANIMAL AND AFTER LIVER DAMAGE BY LIGATION OF COMMON DUCT AND CHOLECYSTECTOMY

Dog No.	Weight in kg.	Per cent quinidin sulphate extracted. a. mg. per 100 cc. b. mg. per dog.	Operation.	Second standardization.	Weight in kg.	Per cent quinidin sulphate extracted. a. mg. per 100 cc. b. mg. per dog.	Rate.	P-R interval increase.	Pathologic findings.	Remarks.
110	13.0	Not done	Chol. and L. of C.D. 8/16/29	19 days later	11.0	Not done	-25%	30%	Parenchymatous degeneration	Died at the end of the experiment.
107	18.8	Not done	Chol. and L. of C.D. 10/1/29	35 days later	16.2	Not done	No change	10%	Dilated bile ducts, slight congestion	Recovered.
†386	9.5	Trace	Chol. and L. of C.D. 12/6/29	23 days later	7.6	4.16 10.9	No change	30%	Moder. fatty change, slight fibrosis	
*411	13.5	Trace	Chol. and L. of C.D. 12/20/29	45 days later	14.5	1.56 5.1	-13%	13%	Congestion, edema, and early fibrosis	Died next day.
483	15.25	1.89 4.9	Chol. and L. of C.D. 1/15/30	16 days later	12.5	3.45 9.0	No change	18%	Early fibrosis, parenchymatous degeneration	Died within 1 hr. after injection.
461	15.0	2.36 6.1	Chol. and L. of C.D. 2/10/30	42 days later	14.0	3.0 9.6	-25%	100%	Fatty degeneration	Died soon after second standardization.
515	16.75	1.42 3.7	Chol. and L. of C.D. 2/15/30	23 days later	15.0	4.29 11.0	Ekg. findings not characteristic; morphin anesthesia	...	Parenchymatous degeneration with necrosis and early cirrhosis	

* The lowest figure (5.1 per cent) obtained upon second standardization in Dog 411 is probably to be explained on the fact that the animal received the quinidin for only 23 minutes, a considerably shorter period of time than in the other animals. It will be recalled that at the initial standardization only a trace of the drug could be recovered. This was probably due to the comparatively short period of injection (23 minutes), and the difficulty in calculating quinidin in concentrations lower than 1 mg. per 100 cc. of blood.

† In Dog 386, the reason for recovering only a trace at the initial standardization was the fact that only 25 cc. of blood were drawn, the quinidin content therein being too small to determine quantitatively.
a refers to mg. per 100 cc. of blood; b refers to the percentage of the amount injected which was calculated to be present in the total blood of the animal at the end of the experiment, figuring the total blood volume as 7 per cent of the body weight.

461, the administration of quinidin after the liver had been damaged resulted in the early production of conduction disturbances with the eventual appearance of ventricular fibrillation (Fig. 1) 22 minutes after the beginning of the injection; whereas, in the same animal before operation, no major disturbances were observed even though the quinidin was administered for 30 minutes.

Comment. The possible elimination of large amounts of quinidin in the bile was of importance. If this was considerable, tying the common duet in the experiments after liver damage would result in the reëntry into the general circulation of the alkaloid that would ordinarily have been eliminated through the common bile duct. An experiment was performed in which an animal was given approximately 1000 mg. of quinidin sulphate dissolved in normal saline over a period of 6 hours through a gastrostomy opening. The common bile duet had been intubated and the gall bladder removed. All the liver bile for the duration of the experiment was collected and a concentration of only 2 mg. of quinidin per 100 cc. of bile was found. In view of the small amount of bile eliminated, the minute amount of quinidin recovered after the introduction of such a large quantity by stomach was ignored in considering our results.

The data from these studies indicate that under the conditions of our experiments there is a decreased tolerance to quinidin after liver injury.

Comparison of the Dog's Tolerance to Quinidin Before and After Eck Fistula With Exclusion of the Liver from the Circulation. This series of experiments was devised to eliminate some of the features which might appear objectionable in the former series. In the present series it was not necessary to consider any significant loss of weight nor were the animals jaundiced.

Method. Dogs were standardized as in the first series of experiments by determining their response to 1 mg. of quinidin sulphate per kilo per minute, injected into the femoral vein for approximately 30 minutes, and then permitted to recover. Several weeks later an Eck fistula was performed according to the method of Fishbach.⁵ The liver was excluded from the circulation by tying the hepatic artery and ligating the portal vein between the Eck fistula and the liver. Immediately after the operation while the dogs were in good condition quinidin was given in the same manner as previously and the results compared. Table 2 shows the findings in 3 dogs before and after the Eck fistula had been made.

Results. From Table 2, it will be seen that in each instance evidence of a decreased tolerance was observed in the animals after production of the Eck fistula. The quinidin concentration of the blood was increased 120 per cent, 160 per cent, and 350 per cent over the pre-operative value. The electrocardiographic responses to quinidin were definitely more marked, occurred earlier, and were more progressive after exclusion of the liver from the circulation, the *P-R* intervals in the 3 dogs being 35 per cent, 75 per cent, and 53 per cent greater and the rate, with one exception, considerably slower. Dog 698 developed notching and widening of the ventricular complexes at 15 minutes and died with ventricular fibrillation at 22 minutes, whereas with the liver intact, it recovered after the quinidin had been given for 27 minutes. Dog 618 developed deformity of the ventricular complexes

TABLE 2.—COMPARISON OF EFFECTS OF QUINIDIN INJECTION IN THE NORMAL ANIMAL AND AFTER ECK FISTULA WITH EXCLUSION OF THE LIVER FROM THE CIRCULATION.

Dog No.	Weight in kg.	Duration of injection (min.)	Per cent quinidin sulphate extracted, a. mg. per 100 cc. b. mg. per dog.	Operation.	Second standardization.	Weight in kg.	Per cent quinidin sulphate extracted, a. mg. per 100 cc. b. mg. per dog.	Rate.	P-R interval increase.	Remarks.
698	15.0	28	1.11 0.3	Eck fistula with exclusion of liver from circulation	9 days later	14.0	3.97 13.9%	Greater decrease in rate	35%	Died at end of experiment due to ventricular fibrillation at second quinidin standardization.
618	16.0	29	1.62 4.1	"	2 mos. later	15.5	4.03 10.8%	10 per cent decrease in rate	75%	Died at end of the experiment due to ventricular fibrillation after getting drug 23 minutes.
10	11.5	30	1.42 3.4	"	6 mos later	17.3	5.4 13.0%	Considerably lower	53%	Animal lived for one hour after the operation.

TABLE 3.—COMPARISON OF EFFECTS OF INJECTION OF QUINIDIN SULPHATE INTO FEMORAL VEIN AND PORTAL VEIN AND FEMORAL VEIN AND FEMORAL ARTERY.*

Dog No.	Weight in kg.	Duration of injection (min.)	Per cent quinidin sulphate extracted, a. mg. per 100 cc. b. mg. per dog.	Second standardization.	Weight in kg.	Method of injection.	Per cent quinidin sulphate extracted, a. mg. per 100 cc. b. mg. per dog.	Duration of injection (min.)	Rate and P-R interval.	Remarks.
70	13.8	35	Not done	36 days later	15.2	Portal vein	Not done	100	Slightly less marked at 30, only slightly more at 60	Animal lived after injection for 100 minutes; quinidin given in jugular vein killed in 8 minutes.
621	13.25	30	1.62 3.9	19 days	12.5	Portal vein	30' 2.21 5.2	60' 4.2 4.9	Same as above	Animal living at end of the experiment.
82	14.5	28	1.08 2.7	4 mos.	20.0	Portal vein	28' 2.35 5.9	60' 2.46 2.7	Same as above	Animal in good condition killed by ether.
102	13.5	29	1.81 4.1	15 days	13.75	Portal vein	29' 1.65 4.0	60' 3.19 3.7	Same as above	Animal in good condition at the end of the experiment.
381	15.25	27	Not done	12 days	14.4	Femoral artery	Not done	27	Less marked in femoral artery injection	
451	15.25	31	1.90 4.3	9 days	14.0	Femoral artery	1.45 3.3	31	Slightly less marked in femoral artery	Maximum electrocardiographic effects noted 45 min. after end of injection.
431	17.0	Not done	Not done	17.0	Femoral artery	25' 3.01 4.2	25	Marked due to greater concentration	Maximum electrocardiographic effects 20 min. after injection, which would tend to show that quinidin was being washed out of capillary bed of leg.

* In Dog 131 injection in femoral artery alone was done to note blood concentration and rapidity of return of electrocardiographic effects.

at 9 minutes, and ventricular fibrillation and death at 27 minutes. Only one dog (Dog 10) was able to survive the calculated amount of quinidin and this animal lived for only an hour after the cessation of its administration.

Comment. These animals were all standardized within an hour after the Eek fistula was instituted. They were in good condition at the beginning of the standardization and the blood sugar was within normal limits at the end of the experiment. It has been shown by Collens, Shelling and Byron³ that the blood sugar, after ligation of the hepatic artery under sodium amytal anesthesia, does not begin to fall appreciably until about 6 hours after the operation. Mann¹² has stated that although autolysis of hepatic tissue results in the formation of products which are extremely toxic, this does not occur to an appreciable degree for several hours after the liver is deprived of its circulation.¹³ In our experiments standardization was performed almost immediately after the operation, too soon for the development of marked alteration in the clinical condition of the animal.

The findings presented appear to indicate that with the liver entirely excluded from the portal circulation, the tolerance of the dog to quinidin is diminished even more than with a damaged liver.

Comparison of the Effects Obtained With the Injection of Quinidin into the Femoral Vein and Portal Vein and Femoral Vein and Femoral Artery.

The method here consisted in first injecting quinidin sulphate (1 per cent solution in normal saline) at the rate of 1 mg. per kilo per minute into the femoral vein of a dog under sodium amytal anesthesia over a period of 30 to 35 minutes, and determining the electrocardiographic changes every minute and the blood quinidin concentration at or near the end of the injection. After several weeks the same animal was subjected to the injection of the same quantity of quinidin per kilo per minute into the portal vein. Observations on the electrocardiographic changes and blood concentration of quinidin were made as in the femoral vein injections and the results of the 2 methods compared.

Results. In Fig. 4, the electrocardiographic effects, that followed both methods of injection in Dog 70 are shown in the form of curves. With injection into the femoral vein, slowing of the rate and prolongation of the *P-R* intervals began to be evident almost immediately and proceeded rapidly. Within 30 minutes the curve for both changes was definitely beginning to straighten out. Injection of the drug through the portal vein yielded similar electrocardiographic effects, though these began slightly later and reached a stationary stage somewhat more slowly: not until the injection had been continued for 50 minutes did the curves become entirely straight.

Ten successful portal vein injections were performed. The results of the three in which blood quinidin concentrations as well as electrocardiographic changes were determined are tabulated in Table 3. In all 10 experiments we were able to give considerably more quinidin through the portal vein than through the femoral vein. By the latter route, the injection of 1 mg. of quinidin per kilo per minute could be continued only once as long as 50 minutes; usually death occurred much sooner. On the other hand, introduction of the drug through the portal vein could be continued for a much longer period without death resulting, in 2 instances for 93 and 100 minutes.

In only 1 instance did the animal die as early as 50 minutes after the injection was begun.

The blood quinidin concentrations in femoral vein and portal vein injections are shown in Table 3. Inasmuch as each determination required at least 100 cc. of blood, it was never possible to obtain more than 2 determinations during any experiment. The figures shown indicate that the blood concentrations of quinidin in mg. per cent after 30 minutes of injection were approximately the same, allowing for the limits of error, in both portal and femoral vein routes. At 60 minutes the mg. per cent of quinidin in the blood after portal vein injection was considerably higher in 2 dogs and slightly so in one than the 30-minute figures. No 60-minute figures could be obtained for a femoral vein injection.

In Table 4 are presented data to show that electrocardiographic changes and considerable concentrations of quinidin in the blood persisted for some time after the termination of the injection through both the femoral and portal veins. Definite electrocardiographic changes were present as long as 50 minutes after the injection was stopped (Dog 103). As much as 2.4 mg. per cent of quinidin sulphate were present in the blood stream 40 minutes after the end of injection. In Dog 475, the electrocardiographic findings were striking. Twenty minutes after stopping the injection, practically no recovery in the rate and *P-R* intervals had taken place; and there were, moreover, periods of apparent intraauricular block which were not in evidence before. The blood quinidin concentration had fallen in 20 minutes only from 3.08 mg. per cent to 2.4 mg. per cent.

TABLE 4.—PERSISTENCE OF ELECTROCARDIOGRAPHIC CHANGES AND BLOOD QUINIDIN CONCENTRATIONS AFTER CESSATION OF INJECTION THROUGH FEMORAL AND PORTAL VEINS.

Dog No.	Duration of injection, minutes.	Vein injected.	Before injection.			At end of injection.			20 min. after end of injection.			40 min. after end of injection.			50 min. after end of injection.		
			<i>P-Rs</i> *	Rate.	<i>P-Rs</i> *	Rate.	Quin. S.†		<i>P-Rs</i> *	Rate.	Quin. S.†	<i>P-Rs</i> *	Rate.	Quin. S.†	<i>P-Rs</i> *	Rate.	Quin. S.†
103	41	Fem.	0.107	200	0.163	111	...		0.126	136	..	0.116	143	..	0.116	150	
75	53	Port.	0.107	167	0.145	130	...		0.132	143	2.4			
475	60	Port.	0.10	176	0.160	96	3.08		0.160	88	2.4						

* *P-Rs*: *P-R* intervals.

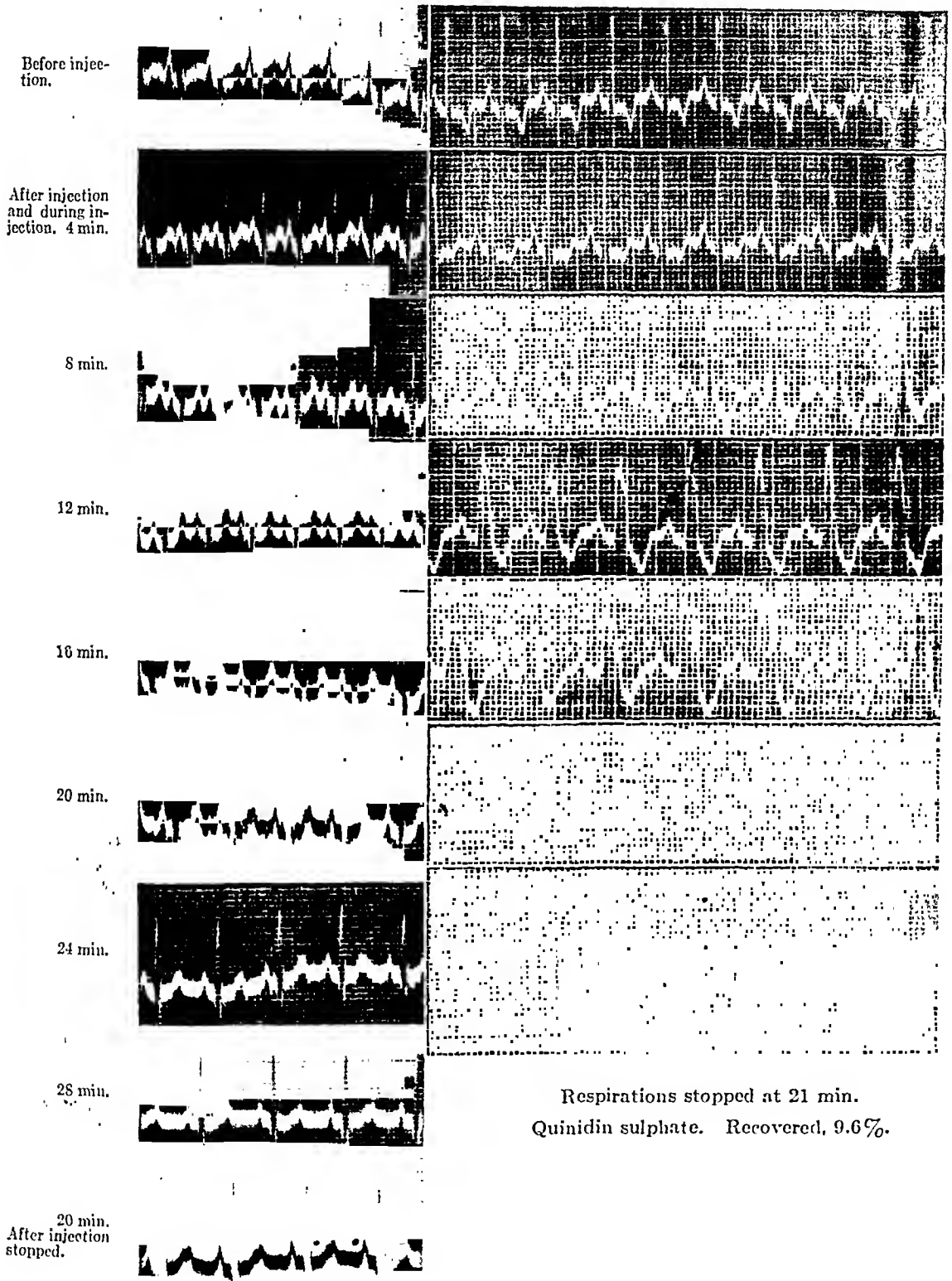
† Quin. S.: Content of quinidin sulphate in the blood in milligrams per cent.

Discussion. That there is a greater tolerance to quinidin when the drug is injected through the portal vein seems evident from the definite fact that much larger quantities of the alkaloid can be introduced through this route. The statement of Roger,¹⁶ that the lethal dose of quinin is considerably greater when introduced through the portal as opposed to a peripheral vein, is true also for quinidin. However, we can find nothing in our experiments which absolutely indicates that this greater tolerance to quinidin is the result of destruction or detoxification of the drug by the liver, as Roger¹⁶ thought to be the case with quinin. The tendency for the blood concentration of quinidin to increase definitely from 30 to 60 minutes during portal vein injection, and particularly the similarity

Dog 461. Operation.—Cholecystectomy and Ligation of Cyst Duct.

Before operation. 1-20-30.

After operation. 3-3-30.



Respirations stopped at 21 min.
Quinidin sulphate. Recovered, 9.6%.

Quinidin sulphate. Recovered, 6.1%.

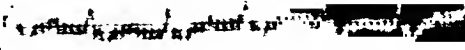
FIG. 1.—Electrocardiograms (Lead II) taken before and after operation (cholecystectomy and ligation of cystic duct). Note difference in electrocardiographic findings after receiving comparable quantities of quinidin intravenously at the various time periods noted. Standardization of normal animal resulted in steady, gradual decrease in the ventricle rate and increase in the P-R intervals. There are no marked changes in the ventricular complex. After operation, note marked decrease in the ventricular rate and early development of conduction disturbances (at 8 minutes) leading to ventricular fibrillation in 24 minutes.

Dog 698. Operation.—Eck Fistula.

Before operation. 3-7-30.

After operation. 3-17-30.

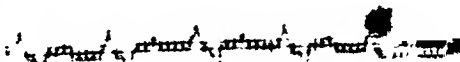
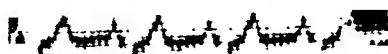
Before injection.
Q. S.



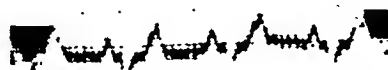
After injection.
4 min.



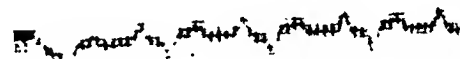
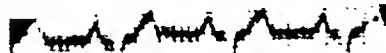
8 min.



12 min.



16 min.



20 min.



24 min.



28 min.



Respirations stopped at 21 min.
Quinidin sulphate. Recovered, 13.9%.

Quinidin sulphate. Recovered, 6.3%.

FIG. 2.—Electrocardiograms (Lead II) taken upon normal animal and after Eck fistula with exclusion of the liver from the circulation. Note steady decrease in the rate and increase in the *P-R* interval as in Fig. 1 before operation. After Eck fistula, note more rapid decrease in rate and early development of conduction disturbances at 12 minutes. Respiration stopped at 21 minutes.

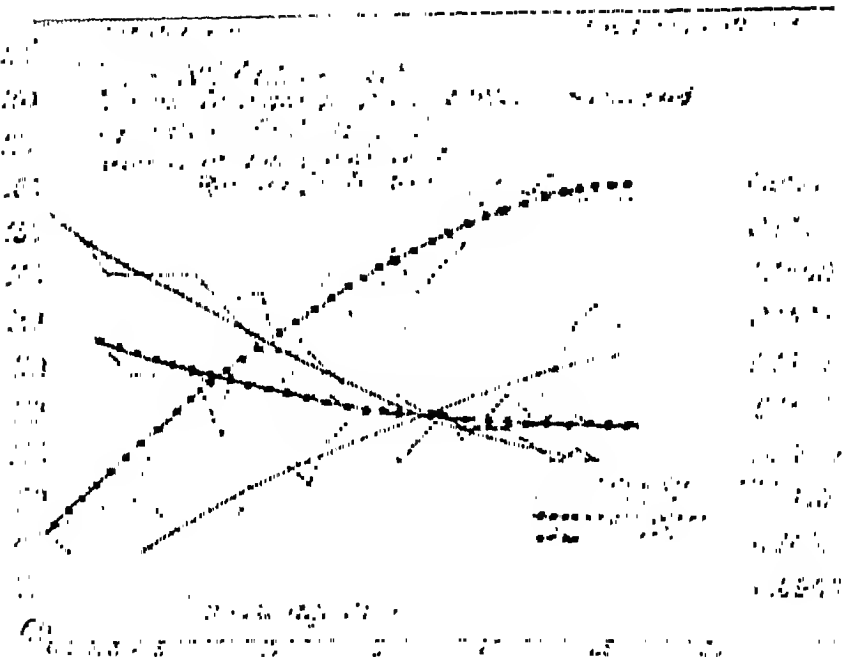


FIG. 3.—Graph showing changes in rate and *P-R* intervals before and after operation. Change in rate before and after operation not marked, probably the result of jaundice. Note marked increase in effect on *P-R* interval after operation.

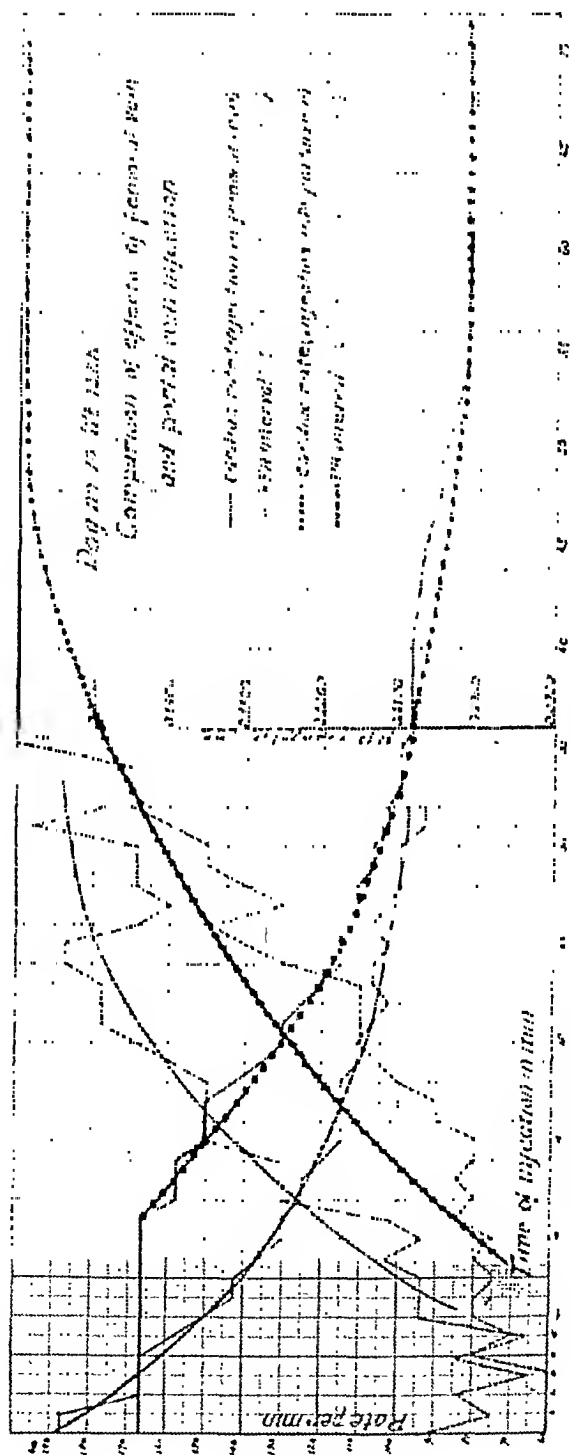


Fig. 4.—Showing electrocardiographic changes after injection in femoral vein and portal vein. Note later inception of electrocardiographic changes after portal vein injection and their more rapid progression until they almost attained the values obtained for femoral vein injection at comparable time periods. Note straightening out of curve at about 50th minute of injection and long duration of injection by portal vein.

of the 30-minute figures for the femoral and portal vein routes, does not suggest greater destruction of quinidin with introduction through the portal vein as the explanation of the greater tolerance to this drug when given by this route. The failure of the electrocardiographic changes to progress after 30 minutes in the portal vein injection does not indicate greater destruction by the liver with administration through this route, for the electrocardiographic changes in femoral vein injections expressed as curves practically paralleled the similar changes in portal vein injections. The presence of relatively high concentrations of quinidin in the blood and the persistence of electrocardiographic changes for a considerable time after the end of injection likewise is evidence not only against a greater destruction of quinidin by the liver with portal vein injection, but also against the conception that quinidin is rapidly destroyed after introduction through any route.

We believe that the obvious increased tolerance in portal vein injections can be validly explained by the interposition of the capillary bed of the liver between the site of injection and the heart and vital centers. With a single injection into the femoral vein the resulting increased blood concentration of quinidin acts directly and immediately upon the heart. Ultimately the capillary beds of the lungs, liver, and other organs have an opportunity to act upon the drug and reduce the blood concentration accordingly. In the portal vein route, the drug is exposed to no new or different capillary beds and we therefore see no reason to expect any difference in the ultimate blood concentrations in either route of injection. There is this difference, however, in the portal vein route, the blood with a suddenly increased quinidin content must pass the liver capillaries before it acts upon the heart and vital centers. The action of the capillaries would be in preventing the heart from being exposed to blood, the quinidin content of which has been suddenly increased.

The chief evidence of our experiments to support this explanation of the increased tolerance to quinidin with portal vein injection was found in the results of the injection of quinidin into the femoral artery, which are presented elsewhere in this paper. Apart from our own experiments, there is considerable additional evidence to support this explanation. The importance of taking into consideration the capillary bed in such comparisons as we are making of the results of portal and peripheral vein injections has been pointed out by several authors.^{9, 12, 21} Moreover, certain work indicates that the capillaries adsorb quinin and quinidin. Hartman and Zila,⁶ Boecker,² and Hatcher and Weiss⁷ have shown that after a single injection of a large dose of quinin or quinidin²⁰ approximately 95 per cent has left the blood stream within 5 minutes. The mere rapidity of this removal would suggest the capillaries as a factor. Moreover, Hatcher and Weiss,⁷ after perfusing the liver with quinidin, readily recovered a considerable proportion of the drug

removed from the perfusate by simply washing out the bloodvessels with normal saline. They interpreted this to indicate that the drug had been removed by the capillaries and that it was held in a more or less loose chemical combination.

The persistence of quinidin effects in the electrocardiogram is interesting. Although we gave large amounts of quinidin, they were usually not lethal. We interpret this as additional evidence against a rapid destruction of quinidin, for if the alkaloid is rapidly destroyed in the tissues or capillaries we would expect the destroyed portion to be quickly replaced and so lower the blood concentration. Granting that destruction is not rapid, it would then indicate that either elimination is not rapid, or, if rapid, that the drug is held very loosely by the capillaries and is readily given up to replace the portion eliminated.

Comparison of Results of Injections Through the Femoral Vein and the Femoral Artery. Our conclusion that the interposition of the capillary bed of the liver rather than any specific destructive or detoxifying action of the liver cells accounted for the greater tolerance to quinidin in the portal injections was further tested by substituting the capillary bed of the leg for that of the liver. As in previous studies the response of dogs to the introduction of 1 mg. of quinidin sulphate per kilo per minute for 30 minutes through the femoral vein was determined by studying the electrocardiographic changes and in one the blood concentration of quinidin. Some days after recovery the injection was repeated through the femoral artery. The latter procedure proved difficult on account of the tendency to thrombosis. However, we obtained two successful experiments, the results of one of which are shown in Table 3.

Results. A considerably larger amount of quinidin given at the rate of 1 mg. per kilo per minute could be given by the femoral artery than by the femoral vein. In one dog, the injection was continued without death of the animal for 1 hour and 40 minutes. The blood quinidin concentration of 1.45 mg. per cent in Dog 451, 31 minutes after the injection had been begun is quite comparable to the figure obtained after femoral vein injection (1.90 mg. per cent) and does not definitely indicate a greater destruction of the drug when it was injected through the femoral artery.

Likewise, after femoral artery injection, there was a striking persistence and even increase in the electrocardiographic effects after cessation of the injection (Table 3). In Dog 431, the electrocardiographic effects progressed for 20 minutes after the injection had been ended, and in Dog 451 the maximum electrocardiographic effects were noted 45 minutes after the injection was completed.

These results are entirely similar to those obtained with portal vein injection and suggest the same explanation of the increased tolerance—the passage of the drug through a capillary bed before it reaches the heart and vital centers acts to save these structures

from the effects of sudden increases in the blood concentration of the drug. The femoral artery injections also suggest that the capillary bed of the leg is almost as efficient as that of the liver in performing this function.

B. Perfusion Experiments. The perfusion experiments reported by Plehn¹⁴ and Hatcher and Weiss⁷ were performed on the isolated cat's liver. Perfusion of the excised liver is somewhat unsatisfactory at best by reason of the differences in pressure in the two blood supplies of the organ and because of the ease with which the liver cells are effected by an artificial environment. These objections are to some degree obviated by using the Knowlton and Starling⁸ heart-lung preparation as a pump.¹⁵ With this method the perfused liver can be maintained in a condition which approximates normal for several hours.

Three series of experiments were performed. The first was the determination in 3 dogs of the degree and rapidity of the disappearance of quinidin from a simple heart-lung preparation. In the next series the disappearance of the drug from the blood in a heart-lung-liver preparation was determined. Concentrations of the alkaloid were likewise estimated in specimens of the liver, lung and heart. The final series of experiments was performed on a heart-lung-hind-leg preparation with the object of determining the effect upon the blood concentration of quinidin of the introduction of a different capillary bed into the circulation.

One typical protocol of each experiment will be presented.

Protocols. Heart-lung Perfusion. After a heart-lung preparation had been established in a dog weighing 14 kilos, which had previously been bled 250 cc., a total of 1000 cc. of defibrinated blood, to which was added a small amount of heparin, was placed in the venous reservoir. Quinidin sulphate (70 mg.) was injected into the tube leading to the superior vena cava during a period of 5 minutes. The heart became slow and irregular, the rate quickly dropping from 120 to 70 per minute. After 5 minutes, the heart became regular at a rate of 80 per minute, the rate gradually returning to the preinjection figure. Specimens of blood amounting to 94, 98, 93, 90 and 102 cc. were removed at 13, 23, 33, 40, and 50 minutes respectively. The heart-lung preparation was still actively functioning when the experiment was terminated.

Findings. The quinidin content of the blood specimens was as follows:

Specimen.	Min. after injection.	Mg. quinidin per 100 cc.
1	15	2.78
2	23	3.11
3	33	2.91
4	40	2.57
5	50	2.77

Heart-lung-liver Perfusion. A heart-lung preparation was set up in a dog weighing 16 kilos with a total of 1450 cc. of defibrinated blood placed in the venous reservoir. The excised liver of a second animal weighing 15 kilos, whose blood had previously been heparinized, was connected through the hepatic artery and portal vein with the heart-lung pump within 2 minutes after the interruption of its circulation. A total of 100 mg. of

quinidin sulphate (1 per cent solution) was injected into the tube leading into the superior vena cava within a period of 5 minutes. Following this injection, the heart slowed from 100 to 72 per minute and the blood pressure fell from 120 to 60. Injection of 3 minims of adrenalin (1 to 1000) quickly abolished these untoward effects. The perfusion was continued for 85 minutes and the heart appeared to be in good condition during the entire period and maintained an average blood flow through the liver of 250 cc. per minute during the duration of the experiment. Specimens of blood of 119, 104, 105, and 116 cc. were removed at 10, 30, 60, and 85 minutes, respectively. Portions of liver weighing 37, 53.5, and 35 gm. were removed at 10, 30, and 95 minutes, respectively. Specimens of lung weighing 25 and 23 gm. were removed at 60 and 85 minutes, respectively. The quinidin concentration of the heart muscle was also determined at the end of the experiment. The total weight of the liver was 407 gm., the lungs 180, and the heart 161 gm. The quinidin content of the various samples are shown in Table 5.

TABLE 5.—CONCENTRATION OF QUINIDIN SULPHATE IN BLOOD, LIVER, LUNGS AND HEART AT VARYING PERIODS AFTER INTRODUCTION OF QUINIDIN INTO A HEART-LUNG-LIVER PREPARATION.

Specimen.	Time after injection, minutes.	Blood conc., mg. per 100 cc.	Liver conc., mg. per 100 gm.	Lung conc., mg. per 100 gm.	Heart conc., mg. per 100 gm.
Dog 1:					
1st	10	1.239	8.692		
2d	30	1.014	8.037		
3d	60	1.147	7.008	
4th	85	1.248	8.409	7.691	3.306

Heart-lung-hind-leg Perfusion. To a heart-lung preparation in a dog weighing 11 kilos and to which 1000 cc. of defibrinated blood was added to the venous reservoir, the hind leg of another heparinized dog weighing 12 kilos was connected through the femoral artery. Quinidin (100 mg.) was injected into the tube leading to the superior vena cava during a period of 10 minutes. Immediately following the injection the heart rate dropped from 130 to 60 per minute and the systolic blood pressure fell from 90 to 60 mm. of mercury. Fairly promptly, however, the blood pressure came back to 80 mm. of mercury and the rate to 120. The bloodflow through the leg averaged 120 cc. per minute during the course of the experiment. Specimens of blood of 103, 105, 104, and 99 cc. were removed at 7, 18, 33, and 60 minutes, respectively. The heart-lung preparation was in good condition at the end of this experiment. Faradic stimulation of the muscle of the leg during the continuance of this experiment caused marked contractions. The leg and heart weighed 690 and 178 gm., respectively.

Findings.

Specimen.	Min. after injection.	Mg. quinidin per 100 cc.
1	7	1.77
2	18	1.65
3	33	1.45
4	60	1.51

Discussion of Results of Perfusion Experiments. Following the introduction of quinidin in a single large dose, there occurred a marked fall in the concentration of the drug within 10 minutes in all our experiments. Estimating the amount of blood in the heart and lung preparation to be 400 cc. and adding this to the 1000 cc. placed in the reservoir, the 70 mg. of quinidin added to this volume of blood would have resulted in a concentration of 5 mg. per 100 cc.

Within a period of 13 minutes, the concentration of quinidin had fallen to 2.78 mg. per 100 cc. In other words, 31.1 mg. (44.4 per cent) had left the blood stream and 38.9 mg. remained.

The more living tissue present the greater is the amount of quinidin removed. The figures for the heart-lung-hind-leg perfusion show that in 7 minutes 75.2 per cent of the injected quinidin had disappeared, and those for the first heart-lung-liver experiment indicate that within 10 minutes approximately 82 per cent had left the blood stream. These figures as well as those from our other experiments are similar to the results obtained by Hartman and Zila,⁶ Boecker,² and Hatcher and Weiss,⁸ who found that most of the quinidin, even as much as 95 per cent of the amount introduced at a single dose into the blood stream of an intact animal, disappeared within 5 minutes.

We believe that the rapid drop in concentration resulted from the drug being held in the capillary bed. The combination can be taken to be a loose one, inasmuch as Hatcher and Weiss⁷ in their experiments were able to recover a considerable quantity of the drug which had disappeared from the blood stream by simply washing out the capillary beds.

After the initial drop in quinidin concentration which occurred within 10 minutes after introduction of the drug, there was no further consistent disappearance of the alkaloid from the blood in our perfusion experiments. Moreover, specimens of liver and lung taken at various periods, as well as a portion of the heart muscle, obtained at the end of the experiment and analyzed for their quinidin content, show that the concentration of quinidin in all these organs remains practically constant during the perfusion. These results lead to the definite conclusion that under the conditions of our experiments the liver does not destroy quinidin over a period of 85 minutes, though it is very active in removing this drug from the blood stream. The behavior of quinidin in our experiments is in marked contrast to that of strychnin in perfusion experiments reported by Priestly, Markowitz and Mann,¹⁵ where a precipitous decrease in the liver concentration of the drug observed during a comparable time interval indicated a destruction of the drug by the liver.

Moreover, the calculation of the total amount of quinidin remaining in the heart, lungs, liver and blood at the end of the experiment (estimated on the figures shown in Table 5 and the known total weights of the organs and the volume of blood) gives figures which account for 70 per cent of the quinidin injected without allowance for the error of the quinidin determination in tissues. The error in the estimation of quinidin in the blood has been shown to be about 10 per cent. In determining the quinidin content of solid organs, our error was even greater. In control experiments, our error was about 30 per cent. This error cannot be ignored and would suggest that practically no quinidin was destroyed during the 1½ hours.

It may be concluded from these experiments that the rôle of the liver in removing quinidin from the blood stream is not specific, but one possessed by any rich capillary bed. The blood quinidin concentration was only slightly higher with the hind leg in the circuit in place of the liver. The difference is satisfactorily explained by the much greater size of the capillary bed of the liver.

If quinidin is not actively or rapidly destroyed, what then is its fate in the body? Our studies give no answer to this question. It is interesting to recall that excretion has been shown by Hartman and Zila⁶ to be important in the case of quinin, they being able to recover as much as 40 per cent of the administered drug in the urine and feces.

Summary. 1. Dogs were found to be much less tolerant to quinidin after their livers were damaged by ligation of the common bile duct and cholecystectomy. This was indicated by the fact that the concentration of quinidin in the blood and the electrocardiographic effects of quinidin were definitely greater after liver damage than before.

2. Exclusion of the liver from the portal circulation (by the institution of an Eck fistula and ligation of portal vein distal to Eck fistula) resulted in a marked decrease in the tolerance of dogs to quinidin. This was shown by the marked postoperative increase in the electrocardiographic effects and the quinidin concentration of the blood, which was high in this type of experiment.

3. The greatly increased tolerance to quinidin when the drug was introduced through the portal vein in contrast to the femoral vein was not the result of a greater destruction of the drug by the liver in the former method of injection. Our own results as well as the results of others suggest that the increased tolerance is to be explained by the fact that in the femoral vein route the alkaloid reaches the heart immediately, whereas in the portal vein injection it must traverse the large capillary bed of the liver before entering the heart: the findings in the femoral artery injections support the evidence of the portal vein experiments that the capillaries protect the heart and vital centers by holding back the quinidin and preventing sudden increases in the blood concentration of the drug. Some evidence is cited to indicate that with portal vein injection the liver capillaries hold quinidin in a loose combination and that after the injection is stopped the alkaloid is apparently slowly given up to the circulation. This evidence also indicates that the action is not specific to the capillaries of the liver but is a property possessed by capillaries as a whole.

4. The results of perfusion experiments on heart-lung, heart-lung-hind-leg, and heart-lung-liver preparations show no indication of destruction of quinidin. Moreover, in the heart-lung-liver perfusions, practically the entire amount of quinidin injected could be accounted for if the amounts recovered from the heart, lungs, liver, and blood were added to the estimated loss of the extraction.

Conclusions. The liver is an important agent in protecting the heart and vital centers against the toxic action of quinidin, though it probably does not act by destroying the alkaloid. The protection is apparently the result of the action of the hepatic capillaries in readily removing quinidin from the blood and holding the drug in a loose combination, thus preventing the drug when taken by mouth from reaching the heart and vital centers in high concentration. This action of the liver capillaries is not specific but is one possessed by other capillaries as well. The great importance of the liver lies in the fact that it constitutes an enormous capillary bed, and in the case of drugs taken by mouth this organ intervenes between the intestines and the heart in the absorptive pathway. Our data indicate that little if any quinidin is destroyed by this organ.

Effective blood concentrations of quinidin in man are apparently small, inasmuch as amounts of as little as 12 grains per day by mouth may produce definite cardiac effects.

If clinical experience should warrant an extension of these conclusions based mainly upon animal experiments to humans, then a diminution of the protective function of the liver, the result of disease, might readily result in a high or rapidly increasing concentration of quinidin in the blood. This would lead to the development of toxic effects upon the heart and vital centers after relatively small doses of the drug.

NOTE.—We wish to express our thanks to Drs. C. G. Johnston, Cecilia Riegel and B. A. Gouley for assistance during the conduct of these experiments.

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THE EFFECT OF ELEVATED METABOLISM ON THE HEARTS OF FRIZZLE FOWL.

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THE Frizzle fowl is a variety of chicken with peculiar upward-turning feathers and a very scanty plumage. One of us has shown that in these birds this entails a profound disturbance in the mechanism of conservation of body heat, and of metabolism.¹ Frizzle fowl exhibits a high basal metabolism and increased food consumption, an almost complete lack of subcutaneous fat deposits, and delayed sexual maturity or decreased fertility. Preliminary observations suggest that adult Frizzles, although their thyroid glands appear to be enlarged, are in a condition of functional hypothyroidism. Further experiments will be carried on to verify this conclusion.

Thus the Frizzle fowl is an experimental animal in which a persistently high metabolism, conditioned by a peripheral factor (lack of plumage), leads to physiologic and anatomic changes in the body economy. They offer a unique opportunity of studying the effect of a permanently high metabolism on the heart. This, of course, has a direct bearing on an understanding of the cardiovascular reactions in human hyperthyroidism. It is still unknown in how far the increased metabolism, as such, or in how far the altered thyroid secretion causes the cardiac disturbances of Graves' disease.

We have studied the heart rates of 21 homozygous Frizzle fowls and of 27 normal chickens of the same approximate age and weight. There are few reports in the literature on the heart rate of chickens. Vierordt in 1877 noted a heart rate of 354.² There is no indication as to his method of counting it. Buchanan,³ using the capillary electrometer, recorded heart rates of 304, 390 and 345 respectively in 3 hens. Stübel,⁴ employing a mercury manometer in the carotid artery, a method which because of the great inertia of the mercury is certainly inaccurate, obtained an average heart rate of 339 in 19 hens, and of 286 in 10 roosters. Kahn,⁵ by means of the electrocardiograph, found rates of 360, 370 and 380 respectively in 3 hens. In all of these experiments the chickens were tied down on a board, and conditions were far from basal. It seems probable, therefore, that all of these counts are too high.

We employed two methods to count the heart rates of chickens. The birds were not tied down or restrained. If one quickly inverts a chicken and places it on its back, and holds it gently on one's lap, it will lie quietly for long periods of time. Placing a black cloth over the chicken's head helps materially to allay restlessness. All of our counts were obtained with the chickens held in this manner. There is no difficulty in keeping a chicken quiet and relaxed for from 20 to 30 minutes. Indeed in some cases we have succeeded in maintaining them at rest in this manner for over 2 hours. Our readings, therefore, were obtained under nearer "basal" conditions than were those of other experimenters.

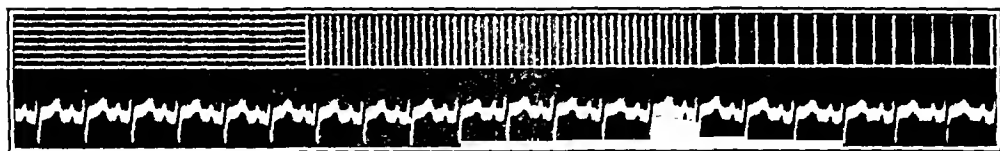


FIG. 1.—Electrocardiogram of normal hen No. 38.

The actual recording of the rate was in most instances made by means of the Victor electrocardiograph with the employment of needle electrodes inserted subcutaneously. The electrode corresponding to the right arm lead in humans was inserted just anterior to the sternal notch; the one corresponding to the left arm lead was inserted over the preeordium. The rate per minute was obtained by counting the number of cardiac cycles in a strip of film corresponding to 6 seconds and multiplying by 10. In a number of cases the rate was counted by means of the cardiotaehometer.⁶ The

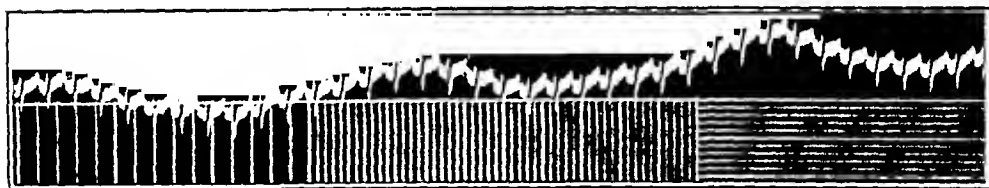


FIG. 2.—Electrocardiogram of Frizzle hen No. 2407.

usual electrodes covered with shaving cream were placed on the chest, one over the preeordium, one just anterior to the episternal notch. The heart beats were recorded by an electromagnetic counter, and readings of the counter were made with the aid of a stop watch.

For normal hens and roosters we found (Table 1) that the average minimum heart rate of 23 hens was 262 ± 30 beats a minute; for 4 roosters 172 ± 19 a minute. These figures are far lower than those previously obtained by other observers because the conditions of our experiments favored the obtaining of more basal rates; under

still more nearly ideal conditions the rates would probably be even lower. Comparison between the initial and final rates in Table 1 suggests that not infrequently we did not succeed in obtaining "basal readings." We did not control the possible effect of previous ingestion of food on the heart rate.

TABLE 1.—THE HEART RATES OF NORMAL FOWLS.

No.	Wt., gm.	Age, mos.	Initial rate per min.	Time resting, min.	Final rate per min.	Time resting, min.	Drop in rate per min.	Mini- mum rate per min.	Remarks.
Females									
1327	1210	14	350	1	290	20	60	290	Struggled once.
2028	1250	13	300	7	250	27	50	250	Quiet.
2714	1250	12	290	1	250	20	40	250	Hen tense.
2710	1250	12	285	0	240	30	45	240	Quiet.
920	1320	25	300	6	260	24	40	260	Quiet.
38	1365	24	260	4	250	22	10	250	Slight movements.
668	1380	23	210	2	180	21	30	180	Quiet.
37	1390	24	290	8	330	26	+40	290	Restless.
128	1405	24	280	1	220	20	60	220	Oceans. movement.
1349	1415	14	370	1	310	21	60	310	Quiet.
654	1420	24	260	3	310	18	+50	260	Slightly restless.
131	1450	24	300	8	270	25	30	270	Quiet.
2141	1450	13	350	4	330	24	20	330	Quiet.
Barrd	1500	14	315	1	240	20	75	240	Quiet.
655	1520	23	310	14	330	31	+20	310	Quiet.
394	1540	23	230	10	220	29	10	220	Quiet.
9705	1560	24	260	22	..	260	Slight movement.
39	1580	24	260	13	240	23	20	240	Restless.
635	1585	23	270	12	270	30	0	270	Restless.
9723	1615	24	250	4	270	22	+20	250	Restless.
9650	1625	24	310	11	290	21	20	290	Quiet.
9528	2150	25	280	5	280	23	0	280	Slightly restless.
9889	2230	24	300	8	270	25	30	270	Quiet.
Av.	1498	..	289 ±38.9	5.6	268 ±37	24	21	262 ±30	
Males									
9920	1385	24	210	5	190	24	20	190	Slight movements.
2661	1535	13	200	6	180	25	20	180	Slight movements.
3317	1575	12	220	4	180	25	40	180	Slight movements.
3107	1675	12	170	3	140	21	30	140	Slight movements.
Av.	1548	..	200 ±18.7	4.5	172 ±19.5	24	27	172 ±19.5	

The average minimum rate of 18 Frizzle hens was 334 ± 43 beats a minute; of 3 roosters 287 ± 12 a minute (Table 2). Thus, as appears more clearly from Table 3, the heart rate of Frizzle hens is on the average 72 beats (27 per cent), and of Frizzle roosters 117.5 beats (68 per cent) above that of normal chickens.

The body temperature of Frizzle fowl under ordinary conditions is the same as that of normal chickens. At environmental temperatures close to or below freezing point the body temperature of

Frizzles, because of excessive heat loss, is slightly subnormal. At the time of our determinations of heart rate the Frizzles were kept in a heated pen, and their body temperatures were undoubtedly normal.

TABLE 2.—THE HEART RATES OF FRIZZLE FOWLS.

No.	Wt., gm.	Age, mos.	Initial rate per min.	Time resting, min.	Final rate per min.	Time resting, min.	Drop rate per min.	Minimum rate per min.	Remarks.
Females									
2392	1085	13	320	3	260	22	60	260	Quiet; quivering slightly.
3238	1305	12	380	2	370	24	10	370	Quiet.
2338	1310	13	350	5	320	22	30	320	Quivering.
2344	1310	13	407	1	310	21	97	310	Quiet.
2407	1450	13	440	5	440	19	0	440	Quiet; moved once.
2386	1545	13	370	7	320	24	50	320	Quiet.
2350	1560	13	300	2	270	23	30	270	Quiet.
3081	1615	12	405	0	375	20	30	375	Quiet.
3062	1690	12	405	7	375	24	30	375	Quiet.
1898	1695	13	320	4	290	22	30	290	Quiet.
2400	1720	13	330	3	290	20	40	290	A, quivering; B, quiet.
9451	1755	25	345	4	345	22	0	345	Slightly restless.
2403	1855	13	370	1	320	18	50	320	A, quivering; B, quiet.
2750	1880	12	330	8	345	27	+15	330	Restless.
2399	1890	13	410	5	340	23	70	340	Quiet.
3222	1930	12	330	8	360	25	+30	330	Quiet.
2119	2145	24	405	5	375	25	30	375	Quiet.
6893	2360	48	360	3	360	22	0	360	Quiet.
Av.	1672	..	365 ±38.8	4	337 ±43.2	22	28	334 ±42.8	
Males									
1901	2100	13	290	7	300	27	+10	290	Restless.
9450	2515	25	320	20	300	29	20	300	Quiet.
2146	2920	24	270	9	270	26	0	270	Quiet; moved once.
Av.	2512	..	293 ±20.5	12	290 ±14.1	27.3	3.3	287 ±12.4	

TABLE 3.—HEART RATES OF NORMAL FOWLS AND FRIZZLE FOWLS.

	No.	Average weight, gm.	Average initial rate per min.	Average minimum rate per min.
Females.				
Normals	23	1498	289 ± 38.9	262 ± 30.0
Frizzles	18	1672	365 ± 38.8	334 ± 42.8
Males.				
Normals	4	1548	200 ± 18.7	172 ± 19.5
Frizzles	3	2512	193 ± 20.5	287 ± 12.4

It is well known that in animals of different species the heart rate is faster the smaller the animal. There is some question as to whether this same rule applies to animals of the same species but of varying size. One of us has shown that in man there is no correla-

tion between body size and shape and heart rate;⁷ and this is also apparently true for fowl (Table 4).

TABLE 4.—BODY WEIGHTS AND HEART RATES.

	No.	Average weight, gm.	Average heart rate per min.
Normals weighing over 1500 gm. . . .	10	1690	263 \pm 25.3
Normals weighing under 1500 gm. . . .	13	1350	262 \pm 37.1
Frizzles weighing over 1700 gm. . . .	8	1942	336 \pm 24.0
Frizzles weighing under 1700 gm. . . .	10	1456	333 \pm 53.0

Pursuing the relation of the high metabolism to the disturbance of heat regulation caused by scanty plumage, we tried to correlate the heart rates of our birds with their amount of plumage. Of 5 birds (Nos. 2350, 2400, 3238, 1901 and 2146) that were fairly well feathered, 3 showed heart rates below the average. However, the observations are too few to allow of a definite conclusion.

It is of some interest to establish whether differences in heart rate between normal and Frizzle chickens already exist at the time of hatching. We have not been able to find observations of the heart rate of newly hatched chicks. The average heart rate for normal newly hatched chicks we found to be 164, and for 7 homozygous Frizzle chicks 163 (Table 5). Thus it is obvious that at hatching

TABLE 5.—THE AVERAGE HEART RATES OF NEWLY HATCHED NORMAL AND HOMOZYGOUS FRIZZLE CHICKS.

Sex.	Normal chicks.			Homozygous Frizzle chicks.		
	Weight, gm.	Time, min.	Average heart rate, per min.	Weight, gm.	Time, min.	Average heart rate per min.
Male . . .	40.7	59	165	39.6	155	163
	38.7	210	167	38.1	62	166
	42.6	241	164	37.8	58	162
Female	39.1	80	163
	32.4	45	165	35.8	102	163
	33.1	46	162	37.6	98	162
	39.3	80	162	39.5	201	161
Average . . .	33.0	223	162	163
	164	163

time there is no difference in heart rate between normal and homozygous Frizzle chicks. The heart rates of these chicks was counted in the following manner: The chicks were taken from the incubator and at once received a subcutaneous injection of 1 cc. of a solution of 0.5 grams of sodium amytal in 125 cc. of distilled water. This induced anesthesia lasting from 45 minutes to 4 hours. As soon as the chicks had relaxed completely, enough of the breast bone was removed with scissors to observe the beat of the heart. This could be done with practically no loss of blood. Counting of the heart beat then was begun at once and was continued until the chick woke up as determined by the first opening of the eyes. Counting was done with the help of a stopwatch and each count was based on the

figure obtained for 20 seconds. After the chicks had fully regained their muscular control they were killed in order to determine their sex. The room temperature during the whole period of observation was between 20° and 21° C.

In each instance it was found that the heart rate was quite fast immediately after the thorax had been opened. Within a very short time, however, the heart rate returned to a lower level, at which it remained with but slight variations during the whole duration of the experiment. Toward the end of the period of anesthesia the chicks frequently made slight movements with their legs, but these movements did not seem to have any significant effect on the heart rate. For each chick the average heart rate was determined for the period beginning with the time when consecutive determinations of the heart rate first became constant and ending at the time when the chicks first opened their eyes again.

In order to show the amount of variation in heart rate during the complete period of observation of individual chicks, one complete record each of a normal and a homozygous Frizzle chick is reproduced in Tables 6 and 7.

TABLE 6.—HEART RATE OF NEWLY HATCHED HOMOZYGOUS FRIZZLE CHICK.

Homozygous Frizzle. ♀ 4818. Weight, 39.5 gm.

3.11 P.M.: 1 cc. sodium amytal solution injected.

3.20 P.M.: thorax opened.

Time.	Heart rate.	Time.	Heart rate..
3.22	189	4.22	165
3.23	189	4.23	165
3.27	186	4.24	165
3.28	174	4.29	165
3.30	174	4.34	165
3.32	171	4.38	165
3.35	165	4.42	165
3.37	165	4.46	165
3.38	159	4.51	165
3.39	159	4.54	162
3.41	159	4.56	159
3.43	162	5.00	156
3.44	165	5.03	165
3.45	165	5.06	165
3.50	165	5.11	165
3.52	165	5.16	168
3.58	165	5.18	162
4.00	165	5.21	165
4.04	165	5.23	165
4.06	165	5.40	165
4.08	165	6.32	156
4.14	165	6.42	165
4.17	168	6.53*	165
4.20	168	6.59	168
4.21	156	7.02	Awake

* Slight movements.

Average heart rate between 3.35 and 6.59 P.M. (204 minutes), 163.8 per minute.

The variations in heart rate are slight, and the fact that the heart rate remained stationary practically to the time when the chicks awoke indicates that it was uninfluenced by the sodium amytal.

TABLE 7.—HEART RATE OF NEWLY HATCHED NORMAL CHICK.

Normal ♀. Weight, 33 gm.

2.16 P.M.: 1 cc. sodium amytal solution injected.

2.59 P.M.: thorax opened.

Time.	Heart rate.	Time.	Heart rate.
3.00	180	4.08	159
3.02	177	4.11	159
3.04	168	4.21	159
3.06	162	4.39	165
3.08	165	4.51	165
3.12	168	5.03	165
3.15	165	5.19	165
3.18	165	5.32*	159
3.21	162	5.41	165
3.26	165	5.53	159
3.32	165	5.57	162
3.37	165	6.08	159
3.42	165	6.21	156
3.46	162	6.30	162
3.49	159	6.40	156
3.52	162	6.49	159
3.57	165	7.00	Awake

* Slight movements.

Average heart rate between 3.06 and 6.49 P.M. (223 minutes), 162.3 per minute.

TABLE 8.—HEART RATE OF NORMAL FEMALE CHICKEN NO. 2710, DURING A PERIOD OF 87 MINUTES OF CONTINUOUS OBSERVATION. HEART RATE RECORDED WITH THE ELECTROCARDIOGRAPH.

Time, min.	Heart rate per min.	Remarks.
0	285	Lying quietly on its back.
15	255	Very quiet.
30	240	Very quiet.
45	240	Has not stirred.
50	240	Quiet.
52	Squawked; moved slightly.
57	270	Quiet.
58	240	Quiet.
59	255	Quiet.
60	240	Quiet.
62	240	Sleeping.
84	Moved.
85	270	
86	285	Frightened.
87	300	Frightened.

In adults the differences in heart rate between the two sexes, both in normal and in Frizzle chickens is very striking, and, as a study of the tables reveals, cannot be explained solely by the greater body weight of the males. The slower heart rate in males is a universal characteristic of all mammals that have been adequately studied. Ellinger,⁸ studying horses, cows, pigs, sheep and goats, found higher rates in females than in males. Thus he observed the average heart rate of 84 stallions to be 28.5, and of 65 mares 33.6 beats a minute; of 12 male pigs 68, of 11 sows 88 a minute; 19 bulls showed a range in heart rate from 40 to 52, whereas the average rate of 94 cows was 81.6 beats a minute. Knoll⁹ established an average heart rate of 58 for 100 bulls, of 75 for 100 cows; and of

73 for 10 male pigs and 82 for 100 sows. He noted that the difference between the sexes first becomes manifest at about the age of 3 months.

In our newly hatched chicks, both normals and Frizzles, there was no difference in the heart rates between the two sexes.

In man, too, females have higher heart rates than males. The basal heart rate of adult males is 61.4 ± 8 , and of females 69.9 ± 9 .⁶

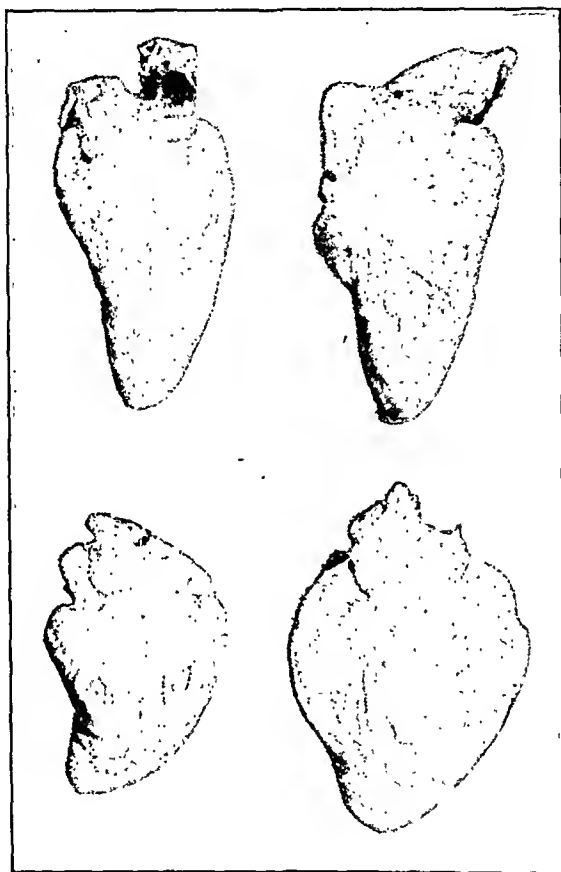


FIG. 3.—Hearts of homozygous Frizzle and normal cockerels at the age of $8\frac{1}{2}$ months. Above: hearts of homozygous Frizzle males. Below: hearts of Leghorn males.

Preliminary observations show that adult Frizzle chickens have a definite hypertrophy of the heart. The heart appears elongated and relatively narrow, the hypertrophy involving chiefly or only the left ventricle (Fig. 3). (A detailed report concerning these changes of the heart will be published later.) These observations seem to show a definite sequence of events: Disturbed heat regulation leading to increased metabolism, which in turn leads to tachycardia, and most probably to an increased minute volume flow of blood, and this finally leads to left ventricular hypertrophy. It is very suggestive that a similar mechanism may be operative in human

hyperthyroidism, except that here the stimulus to the increased metabolism is found in some intrinsic functional disturbance.

A number of observations that were made incidental to the chief aim of our study merit more detailed mention. In all of the chickens we observed a marked lability of heart rate. This is well illustrated in Table 8; as well as in Figs. 4 and 5. The graphs represent

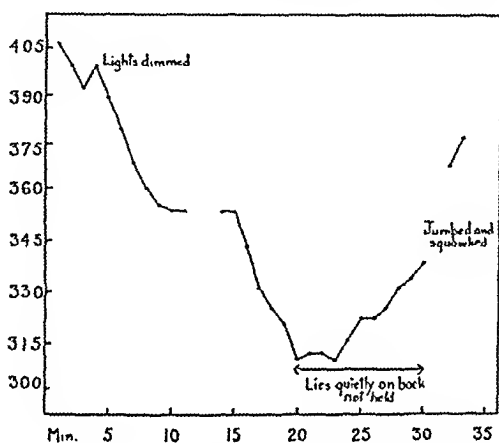


FIG. 4.—Heart rate of Frizzle, No. 2344, recorded with cardiotaehometer. Room temperature, 17° C.

continuous observations with the cardiotaehometer of the heart rate of Frizzle chicken No. 2344. Fig. 4 is a 33-minute run when the room temperature was 17° C. Fig. 5 represents observations of the heart rate while the chicken was held on the observers lap before an open fire. In addition to these major variations in rate which correspond to those observed in man⁶ we frequently noted a distinct sinus irregularity when the chicken was relaxed and breathing quietly.



FIG. 5.—Heart rate of Frizzle, No. 2344, recorded with cardiotaehometer while resting before open fire.

Our data on the cardiovascular reactions of Frizzle fowl throw a certain light on the cardiovascular reactions of patients with hyperthyroidism. While a number of recent experiments seem to show definitely that an excess thyroid secretion may in itself through a direct action on the heart provoke a tachycardia,¹⁰ the effect of an increased metabolic rate in increasing the work of the heart cannot

be ignored. The increased oxygen utilization by the tissues necessitates an increased minute volume flow of blood. This is accomplished by an increased output of the ventricles per beat as well as by an accelerated heart rate. It has been estimated that in Graves' disease the work of the heart may be increased by as much as 250 per cent.¹¹

A clinical condition analogous to that found in Frizzle fowl, characterized by an increased metabolic rate unassociated with hyperthyroidism, is found in chronic lymphatic leukemia. Minot and Means¹² showed that the amount of pulse elevation for a given metabolic rate was essentially the same in hyperthyroidism and in chronic leukemia. Moreover, the hearts of leukemic patients that were examined postmortem were on the average 75 gm. overweight. It is true that more recently Friedgood¹³ reached the conclusion that in chronic lymphatic leukemia the pulse rate is not entirely dependent on the basal metabolic rate, because in his patients high metabolic rates were accompanied by relatively small increases in heart rate.

In Frizzle fowl it seems clear that the elevated metabolism is the cause of the rapid heart rate, and that the increased work of the heart causes cardiac hypertrophy. Indeed, it seems that more serious injury to the heart may result. One of the Frizzle roosters who was not included in Table 2, exhibited an unusual form of heart block. Furthermore, we have observed that when Frizzle chickens are carried in the usual way by the legs with the head down sudden death at times ensues.

Summary. The Frizzle fowl, a variety of chicken with scanty plumage offers an opportunity of studying the effect of a greatly increased basal metabolism as such on the heart. In these birds the scanty plumage entails a profound disturbance in the mechanism of conservation of body heat with a resulting high metabolism.

The heart rates of 27 normal breeds and of 21 homozygous Frizzle fowl were studied by means of the electrocardiograph and the cardiotaehometer.

The average minimum heart rates of normal hens was 262 ± 30 and of Frizzle hens 334 ± 43 beats a minute; of normal roosters 172 ± 19 and of Frizzle roosters 287 ± 12 beats a minute.

The average heart rates of both normal and Frizzle chicks of both sexes at birth was the same, about 164 beats a minute.

The rapid heart rate of Frizzle fowl is conditioned apparently only by their high metabolism.

Preliminary observations suggest that the hearts of Frizzle fowl are larger than those of normal chickens of the same age and weight.

All of these observations suggest that a persistently elevated basal metabolism, as such, may cause tachycardia, cardiac hypertrophy, and possibly other functional and organic damage to the heart.

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STUDIES OF HUMAN CAPILLARIES.*

PRESENT DAY TECHNIQUE FOR THE STUDY OF HUMAN CAPILLARIES.

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THE purpose of this article is to present the most satisfactory methods of studying the capillary circulation of the nailfold in human beings. We shall attempt to present a technique and describe apparatus by which such studies may be carried out under as nearly normal and standard conditions as possible.

Since the work of Von Kries¹ in 1875 and Roy and Brown² in 1878, advances have been made in the methods and the apparatus for this study. Hueter³ in 1879 observed the capillaries in the mucous membrane of the human lip through a glass slide pressed against the lip and a low power lens of about 25 magnifications. Lombard⁴ in 1911 was able to make a better study of these vessels with the

* Aided by grants from the Harriet Weil Fund, The Oliver Rea Fund, the Josiah Macy, Jr., Foundation and the General Medical Research Fund of the New York Post-graduate Medical School.

use of artificial lighting and higher magnifications. In 1916 Weiss⁵ made a valuable contribution to this study by recording his observations photographically. Since permanent records are of the utmost importance in studying the capillaries, the first part of this paper will be devoted to photographic technique. The second part will be a discussion of methods for the determination of the capillary pressure, the temperature of the capillary fields, the fragility and permeability of the capillaries and the rate of flow within them.

Photography. In photographing the capillaries of the skin and mucous membranes the following points should be considered:

1. Short exposure.
2. Immobilization of the field.
3. Sufficient cool light applied at the correct angle of incidence and the utilization of as much of this light as possible.
4. A rapid film sensitive to slight color contrasts.

The chief requirement in photography is for an exposure of $\frac{1}{5}$ of a second, or better $\frac{1}{10}$ to $\frac{1}{25}$ of a second. Slower exposure does not produce a sharp definition of the capillary loop if the magnification is sufficient to be of value, because of the almost constant motion of the vessels. This motion consists of movements of the vessels themselves in all directions, combined with involuntary muscular movements of the extremity, including tremors, and, in many instances, transmitted cardiac impulses. The varying size of the corpuscle stream also causes changes in the contour of the vessels.

Satisfactory immobilization of the part to be studied is a difficult problem. It is readily realized that only gross variations in the position of the part can be controlled. Any apparatus which would control even these movements to a marked degree would exert such pressure on the vessels that normal conditions would no longer exist. A small metal vise (Fig. 3) may be used to steady the finger or plasticine may be employed where extreme steadiness is necessary. If only slight pressure is applied with this to the sides of the finger there is no apparent effect on the circulation to the nailfold capillaries. The arm may be comfortably supported in a wooden trough lined with a soft padding; or the foot may be placed on padded blocks. Any part studied should be so placed that it is on a level with the heart. With the patient comfortably arranged, the entire nailfold area is best studied by moving the microscope across the field with a ratchet and pinion system instead of moving the stage, as is the conventional procedure. In this manner voluntary tensions are avoided and there is less involuntary twitching. We have found no mention in the literature of such an arrangement for this particular purpose and it has greatly increased the ease of controlling the field. The use of a faster film, smaller film surface and more light has made the entire problem of immobilization less important than when exposures of several seconds were necessary.

The tungsten bulb and the carbon arc have both been employed as sources of light. Callender⁶ in 1925 described a method employing a 1000-watt Edison lamp in an Edison lamphouse. He obtained magnifications ranging from 16 to 61 diameters and made exposures of 12 to 15 seconds. We have used a small bulb with a very concentrated tungsten filament, filtering the rays through a colored heat-absorbing glass and condensing them with a lens system. This method provides sufficient cool light for visualization but not for satisfactory photography.

An automatically fed pencil carbon arc, obtaining its current of 5 amps. at 60 V. through a resistance on a 110 V. line, supplies an abundance of light for photographic purposes. The rays from the carbon arc are focused through a lens system in the lamp and are then passed through a water filter so that they illuminate an area of about 2 sq. cm. A color filter is interposed in the system to give better contrast. This may be in the form of a dye in the water filter or a thin colored glass or strip of celluloid, the latter two allowing easy changing of colors to meet different circumstances. Green has proven the most satisfactory for both observation and photography. If the water filter is thick enough, a thermocouple temperature reading after 15 minutes of continuous observation shows less than 1° C. rise in temperature over the area studied. Weiss⁵ in 1916 used a similar method. His time of exposure was from $\frac{3}{4}$ to 1 second. Sheard⁷ in 1924 and Sheard and Brown⁸ in 1925, still using this oblique system of illumination and momentarily increasing the brilliancy of the light at the time of exposure, were able to increase the time to $\frac{1}{1000}$ of a second. It is evident, however, that the extreme degree of light destroyed some of the contrast.

The angle of incidence of the light rays is another factor of utmost importance in obtaining efficient illumination. In our earlier studies the rays were directed on the field at an angle of 45° and from one side only. In all such systems there is a great loss of light and shadows are cast, distorting the appearance of the capillaries. Crawford and Rosenberger⁹ in their "Cinematographic Observations of the Human Capillaries" used an opaque illuminator to obtain almost vertical illumination. In this system the rays are focused on the field through the lens system of the microscope, and refraction is overcome with a light polarizer. We have found that the "Ultropak" system (developed originally for metallurgy and adapted for capillary studies and other microscopic work by E. Leitz & Co.) to be the most practical form of illumination used with the condensed rays of a pencil carbon arc lamp as previously described. With this equipment it has been possible to study in detail minute structures, such as intercapillary anastomoses,¹⁰ which have hitherto been observed only with extreme difficulty.

The standard 35-mm. film permits a concentrated image and makes possible short exposures. Larger film surfaces necessitate

the spreading of the small amount of light over greater areas, thereby increasing the time of exposure. Any exposure greater than $\frac{1}{2}$ of a second where magnifications of 176 times are used results in a blurring due to movements already described.

A superspeed film makes possible a rapid exposure even with the interposition of a rather dense color filter. Through the courtesy of the Du Pont Pathé Company we have obtained a panchromatic film which is about seven times faster than the average panchromatic film. This seems to give better results than an orthochromatic film even with a green filter system. Such film must be handled in complete darkness both in loading the camera spools and in developing it. In special instances it may be "speeded up" by sensitizing

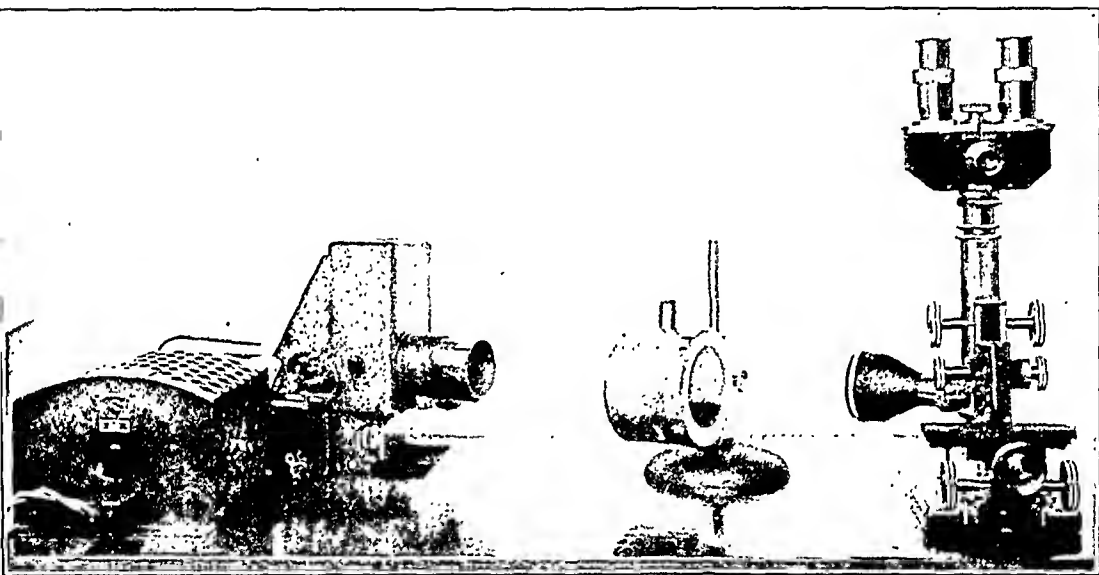


FIG. 1.—The Ultropak is attached to the tube of the binocular microscope and is adapted to receive the rays from the carbon arc, which is located in a well on the left side of the table. A water filter, containing a green dye, is located between the two. The ratchet and pinion arrangement at the base of the microscope will move the tube of the scope either forward and backward or from side to side.

it just before use with one of the several methods in common practice, such as washing in distilled water and quickly drying. Since enlargements are desirable a developer should be used to give as fine a grain to the negative as possible. The Leitz enlarging camera (Fig. 2), built especially for 35-mm. film, produces excellent 4 by 5 inch size records for preservation.

The camera used to carry this film is a Leica. The spools hold sufficient film for about 30 exposures. A conical metal apron extends from the front of the camera and its outer end attaches to the ocular of the microscope. Within this outer end of the apron is a shutter with cable release and a prism which directs some of the rays at right angles through a focusing tube. At the instant of

exposure this prism is swung aside with a cable release making all of the rays available. The lens system of the capillarscope replaces that of the camera (Fig. 3).

The preparation of the field for either observation or photography is very important. Gentle cleansing with a soft brush and soap and water at body temperature removes dirt and dead epithelium. Thorough drying and removal of grease with xylol before oil is applied gives a clearness sufficient for most work. Fifteen minutes should then elapse before examination to insure a return of the vessels to their normal status. The irritation thus produced is

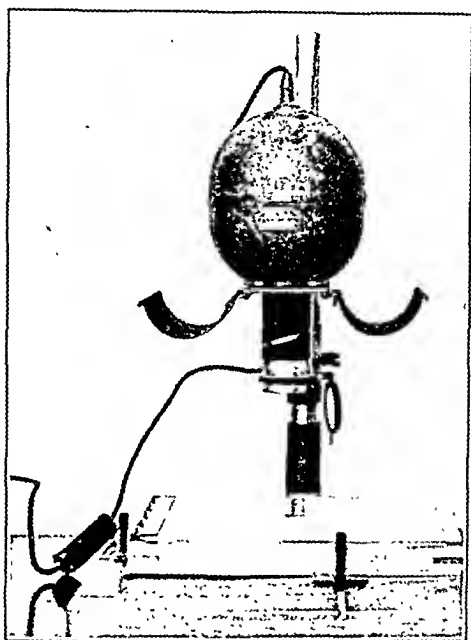


FIG. 2.—Camera made for enlarging 35-mm. cinema film by E. Leitz & Co. The filter swung at right angles to the lens tube is amber glass and allows focusing of the negative directly on the bromid paper.

much less than that caused by blistering with cantharides, heat, or by the mechanical removal of the superficial layers of the epithelium with a razor. It is true that these methods give a clearer field and that the capillaries stand out much more clearly. There is definitely less haze than with the simple cleansing method but an abnormal condition is produced by these other methods and we have attempted to study these vessels under as nearly normal conditions as possible. A bland clear oil, such as white mineral oil, cedar oil, or castor oil, is applied to the skin, diminishing the refraction due to the unevenness of the outer layer of epithelium. Unna¹¹ in 1891 suggested the use of oil for this purpose. Schur¹² suggests the placing

of a small cover glass over the oil. We have found that this prevents the oil from running off the field. In some instances where patients perspire freely and in very warm weather, the moisture mixing with the oil produces an emulsion, resulting in a haze which obscures the field. This difficulty is not easily overcome, as preparations used to reduce perspiration create an abnormal condition.

It is important that the patient be placed in as comfortable a position as possible and that the operator be free to study the capillary area. It is also important for standardization that the areas studied should be on the same level as the heart. Fig. 1 shows the apparatus set up on a table especially constructed for studying the vessels of the finger-nail beds. The patient sits across from the

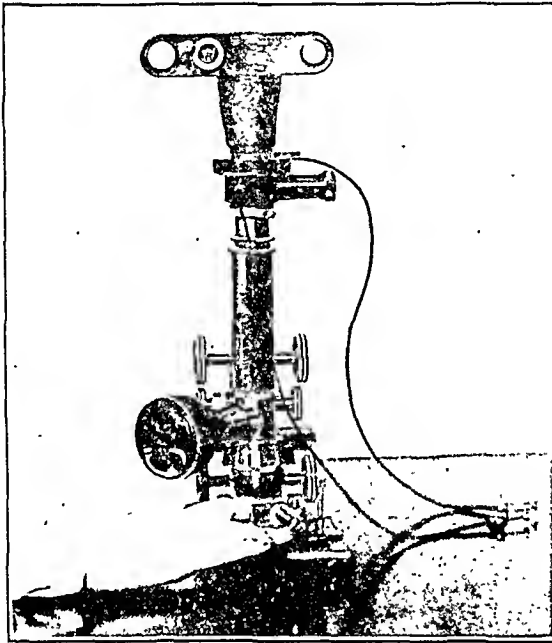


FIG. 3.—This shows the Leica camera fitted to the ocular of the capillarscope. It also shows a simple finger rest for maintaining the position of the finger.

operator and the height of the table is such that the hand is at the heart level. If the table is placed opposite the average hospital bed the same conditions exist. The lamp is placed in a well on the table so that the rays will enter the Ultropak at right angles to its mirror.

Figs. 4 and 5 are illustrations of unretouched photographs of capillaries in the finger-nail bed as taken with the apparatus described above.

We have not discussed the problems of cinematography of the capillaries for the following reasons: (1) It necessitates the use of very expensive and elaborate equipment; (2) such equipment requires technical knowledge beyond that of the average investi-

gator; (3) it is not practical for the study and the obtaining of permanent records in a large series of cases.

We appreciate, however, that such studies give valuable information regarding changes in the blood flow and capillary appearance.

Capillary Pressure. The pressure in the smaller vessels and capillaries has long been a matter of interest. Von Kries¹ first attempted to measure this by applying a glass slide to the skin and noting the amount of pressure necessary to produce pallor. Danzer and

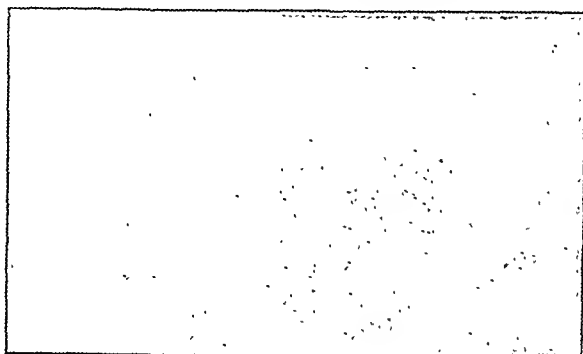


FIG. 4.

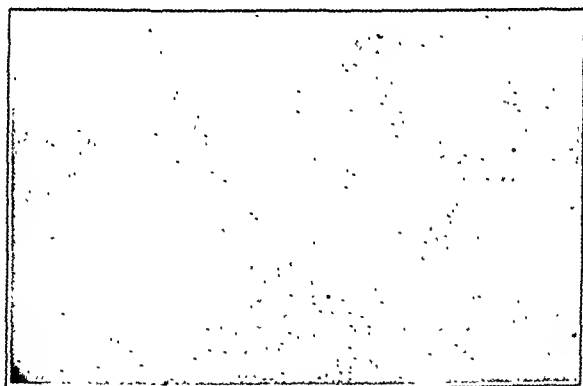


FIG. 5.

Figs. 4 and 5.—Unretouched photographs of capillaries in the finger-nail bed made with the apparatus described. The magnification on the original 35-mm. cinema film is 176 times. The enlargements shown are about 4 times the size of the original film.

Hooker¹³ and Kylin¹⁴ found that blood continued to flow even when pallor was present. The Danzer and Hooker apparatus (Fig. 6) consists of a mercury manometer connected to an air chamber between a flexible transparent membrane and a glass slide. The glass slide is held in a fixed position and the flexible membrane is brought in contact with the capillary bed. The capillaries are observed with a capillarscope, through both the slide and the membrane while air is forced into the chamber. As the flow in the vessels starts or stops the pressure can be read in millimeters of

mercury. Observations must be continued for some seconds as the flow in even major capillaries often starts or stops without pressure being applied. The point at which the flow starts on releasing the pressure has been considered the preferred one to be recorded. Such a reading gives only a general average for the area observed or for a particular capillary. A method recently described by Str  x and Degraff¹⁵—a modification of the Danzer and Hooker method—uses a weight balanced against a spring and one observes the vessels through a glass window for the condition of the flow. It is simpler than that devised by Danzer and Hooker but it has not been sufficiently tested. Landis¹⁶ by actually inserting pipettes of drawn quartz into the arterial and venous limbs of the capillary as well as into the tip of the loop has shown different pressures at

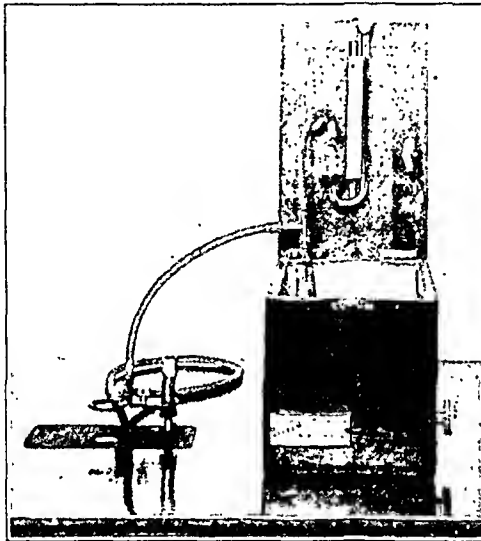


FIG. 6.—Capillary pressure measuring apparatus as devised by Danzer and Hooker. The air chamber, connected by tubing with the manometer, is seen to the left of the case. This is placed beneath the objective of the capillarscope.

these various locations, the greater being in the arterial limb and the lesser in the venous, a downward gradient of pressure being present. The technique of this procedure is much too difficult for general work and we feel that the apparatus of Danzer and Hooker gives the most satisfactory results of any yet devised that may be used in routine work.

Skin Temperature. The skin temperature of a capillary area studied may be determined in several ways. We have found that an approximate reading can be obtained by using a mercury thermometer with a flattened bulb and an insulating grip. Such a type has been developed by Becton and Dickinson & Co. for Horton of the Mayo Clinic. The flattened bulb is placed against the skin and the mercury registers from two to three minutes. Variations in pressure on the skin by the bulb affect these readings.

A much more accurate, reliable and responsive instrument depends on the principle of the thermocouple. Variations in the temperature of the couple cause varying amounts of electric current to be set up in direct ratio with the amount of variation in temperature. These slight currents are matched against known currents with a potentiometer. We have been using an instrument developed by Leeds and Northrup (Fig. 7) in which adjustments of the potentiometer to bring the galvanometer to balance give a reading directly on an attached scale of the temperature in both Fahrenheit and Centigrade.

The thermocouple may be fastened to an area and repeated readings made. A special couple placed at the tip of a hypodermic

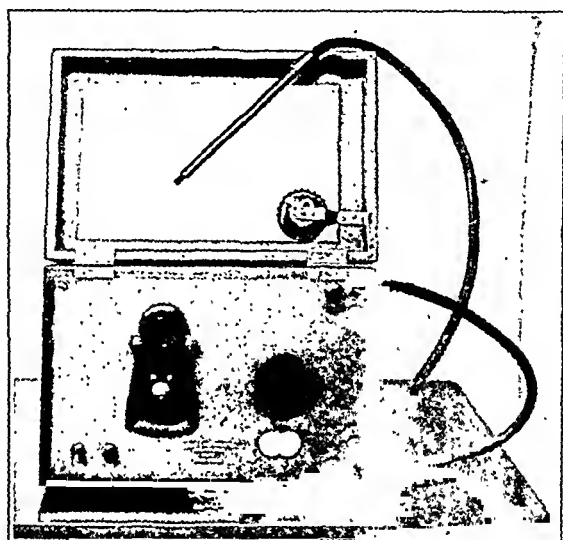


FIG. 7.—Leeds and Northrup potentiometer indicator. The fine wires of the thermocouple can be seen at the tip of the composition rod. The scale calibrated in both Centigrade and Fahrenheit, is seen below the knob of the potentiometer or slide wire. The wedge-shaped instrument is the galvanometer.

needle is used for recording temperatures beneath the skin surface. Leeds and Northrup also supply an apparatus for electrically recording these temperatures. Such apparatus provides permanent graphic records and is of value where studies are being made of temperature changes over a certain area during a given period.

Capillary Permeability and Fragility. Capillary permeability was first determined by Gänzzlen¹⁷ by the blister method as will be described in another paper. Subsequent workers^{18,19} have added to this subject. At the present time there are no reliable methods available for the accurate determination of capillary permeability in humans. Cutter and Marquard²⁰ have shown that by producing a sufficient negative pressure over a capillary bed the vessels will rupture and the blood will appear around them.

This fragility of the human capillaries is another interesting problem for further studies, especially in the purpuric diseases.

Rate of Blood Flow. Studies of the actual rate of the flow of the blood through the capillaries are of little value because of the extreme variation in different vessels and from second to second in the same vessel.

Relative Time of Flow and Stagnation. We are using a rather crude but simple procedure which we have called the "Two Minute Flow Test" to help us determine the amount of time the blood is actually flowing through the capillary loop being observed. A vessel is observed during a 2-minute period and the number of seconds of stoppage and of flow are noted. An average of 10 counts, taken from the larger capillaries in which the blood is present at all times, is accepted as the flow-test figure for that particular trial. Under average normal conditions in an average individual the blood will often cease to flow for a total of from 10 to 20 seconds of the 2 minutes.

Conclusion. An attempt has been made briefly to sum up various methods and the apparatus involved for the study of the capillaries. We believe that the Ultropak method of illumination has made the observation and photography of these vessels very much easier and more satisfactory. The areas in which human capillaries are accessible for detailed study under normal conditions are few. Further improvement in both apparatus and methods is desirable. Some of the procedures have simply been mentioned. Studies are now being made for the further development of these and of the apparatus involved.

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SELF-MUTILATION IN CHRONIC ENCEPHALITIS.

AVULSION OF BOTH EYEBALLS AND EXTRACTION OF TEETH.

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"Rash man how could'st thou bear to outrage so Thine eyes?
What Power was it, what wrought on thee?"—*King Æpidus*.

Case Report. H. V., a high-school girl, aged 16 years, of Russian-Jewish parentage, was born in New York, in 1915. The personal and family history was given by the mother, an intelligent woman.

Birth was at full term, and delivery spontaneous. The infant and early childhood years were those of a physically and mentally healthy child, differing in no significant features from those of the other members of the family of normal children. She began school at the age of 6 years and was considered in all respects a good pupil until the grade of 4B; at this time the scholastic standing lapsed.

The history of infectious diseases incidental to early years records measles at 4 years, complicated by one convulsion. There was no continued drowsiness or somnolence, no paralysis and no other symptoms suggestive of encephalitis. Recovery was apparently complete. At the age of 5 years she had an attack of chickenpox of short duration, the course a normal one without neuropsychiatric complications. In her 6th year she sustained a trauma from falling down five steps injuring her head and back. No serious results seem to have followed; she was not unconscious at the time, did not bleed from the nose or ears and there were no persistent complaints—no headache, no dizziness or convulsions.

In short, up to the time of the beginning of the present illness, the girl was evidently normal, without neuropathic taint inherited or acquired. Her menses began at the age of 13 years and were regular and normal. She was sociable, indulged in the usual play activities, was in no way peculiar or seclusive, showed no temper tantrums, no unusual attachment to members of her family. She was balanced in behavior, well thought of by other children and adults and regarded as a rather clever child.

At the age of 8 years, in February, 1923, the patient passed through a febrile attack. The details of this period of illness are vague. The records at the Neurological Institute, where she was treated at the time, showed that the illness was regarded as of the nature of influenza; the details upon which the diagnosis was made are not clearly defined in the hospital records. The significance of this period of illness is made the more evident by the recorded information that the child was in "perfect health for a year," although she developed "weakness of the eyes"—she found it more difficult to read, but correction of vision was obtained by glasses. During this period her left arm began to "draw up" and she "walked with a limp."

Early in 1924 she was admitted to the Mt. Sinai Hospital; here a left hemiparkinsonian motor syndrome was noted and also pathologic ocular signs. The pupils were unequal, right larger than left; both reacted well to light but accommodation was absent in the right and sluggish in the left eye. Four injections of foreign protein (typhoid vaccine) made no impression upon the symptoms. Following discharge from the hospital, the girl returned to school.

It was observed at this period that the patient would fall asleep in the classroom and at home and she complained of being unable to do her school work. There was no nocturnal wakefulness. She improved somewhat, and for the subsequent 4 years the somnolent tendency seemed to diminish.

In 1928 she was admitted to the Neurological Institute and the following was recorded: Staring facies, left spastic gait, left arm flexed and with marked tremor, deep reflexes increased on the left side, slight inward squint of the left eye and deviation of the tongue to the left. An encephalogram taken at that time showed very little air entering the ventricles, nearly all of it distributed over the cortex. The latter finding was at the time interpreted as "suggestive of lack of cortical development, possibly dehydration." The blood and spinal fluid Wassermann tests were negative. The diagnosis at the time was chronic epidemic encephalitis.

After leaving the Neurological Institute the patient returned to school and was in the 8th grade; she entered high school but her work was unsatisfactory; she was lacking in concentration and sustained effort. She also complained of "spasm of her eyelids," making it difficult for her to keep her eyes open.

At this time she began to show changes in personality and became a behavior problem at home. She often prevaricated and had frequent temper tantrums in which she would tear her clothing and strike her mother. When confronted with the results of her destructive conduct, she readily admitted her misdoings and said that "she could not help it." On a number of occasions she broke windows in the house during these explosive episodes; at times, these were in reaction to no evident situation; occasionally these tantrums would be followed by an hour of somnolence. She frequently became remorseful and would spontaneously reiterate "Why do I do it? Why do I do it? I can't help it." She would readily strike her sisters when they interfered with her desires or angered her. Her school-work was nevertheless good.

At about this time, that is, 3 years before admission to Morrisania Hospital, she would occasionally lock herself in the bathroom and appear a short while after, bleeding from the mouth and with teeth missing. She admitted extracting her teeth and said that she "could not help taking them out." Her parents recall that she would anxiously remain up awaiting the retirement of the members of the family, seeking the opportunity to sequester herself in the bathroom and to yield to this imperious desire to extract her teeth. In this way she took out all but 9 of her teeth.

She developed Vincent's angina after these repeated extractions, and was admitted to Bellevue Hospital in March, 1931, where 7 more of her teeth were extracted by the dentist. Upon admission to the Morrisania Hospital, July 30, 1931, her 2 remaining teeth were removed because of infection.

She was admitted to the Morrisania Hospital because of some swelling and redness of the right eye. The mother noticed that she had been rubbing that eye during the day and there was some swelling and bulging. Her temperature was 100° F.; pulse, 100; respirations, 22. She was examined by one of the house physicians, put to bed, her eye washed with boric acid and an ice-bag was applied. She was quiet and apparently slept until 3.20 A.M., July 31.

The nurse in charge of the ward stated as follows: "I was notified by an attendant that this patient's eye had fallen out. I immediately went to the patient, and found that she was holding her right eye in her hand and on questioning her she said that it had spontaneously fallen out while she was sleeping. She answered all my questions unhesitatingly and appeared intelligent. She did not complain of any pain or discomfort. Her actions were quite normal except for her seeming indifference toward the incident. She did not seem in the least disturbed. At 7 A.M. she was seen lying in bed, the left eye looked normal. The right socket was dressed. At 8.45 A.M., on July 31, the patient suddenly shouted that her left eye had fallen out. The left eye was found in the bed on the patient's left side. There was only slight bleeding from the sockets. She did not complain of pain and seemed to be lying quietly without any particular emotional display." She was examined the next morning by a neuropsychiatrist who found a young blind girl, aged 16 years, with a left extrapyramidal hemiplegia, showing no particular emotional display and cooperative for all details of examination. She denied gouging out her own eyes. She was well oriented. Remote memory was good. She, however, insisted that she did not remember the details of that particular period when her eyes "popped out." There was no intellectual defect. She seemed to be of normal mental standard. Sensory examination was entirely normal.

During her further stay in the hospital the patient rubbed her right cheek until it bled and bit deeply into her tongue. Spinal fluid examination on August 4, 1931, showed a bloody tap which was probably traumatic. The eyes were enucleated almost intact. The eye muscles in both eyes were torn at the tendons in some cases and somewhat beyond the tendons in other muscles. The anterior chamber was free, sclera intact, conjunctiva covered both eyeballs. The optic nerves were also avulsed. The right optic nerve was attached to the eyeball, was 1 inch long and the left was 2 inches long. The cornea were somewhat cloudy. The ophthalmic surgeons indicated that the enucleation was complete with the delivery of 2 intact eyeballs. Roentgen ray examination of the skull showed rounded shadows in each orbit due to blood clot, but no change in the bone. The upper right first and second molars were removed in the hospital, leaving the patient edentulous. The sockets of these teeth were infected and the teeth loose. The other teeth were missing on admission. In October, 1931, she was admitted to the Montefiore Hospital. During the first few weeks of her stay there the patient repeatedly attempted to injure herself, picked at the dressings over her sockets and carefully watched over the skin of her face. The patient was restrained and carefully watched. No further self-mutilation has been observed for about a month following her admission to the Montefiore Hospital.

Physical examination at the Montefiore Hospital showed an edentulous, undernourished young girl, aged 16 years, both eyes missing, there having been complete enucleation of eyeballs bilaterally. There was no mouth infection. Neurologically, she showed a left extrapyramidal hemiplegia, no Babinski, cogwheel rigidity on the left, uniform atrophy of the left upper and lower limbs. There was left hyperreflexia except for the ankle jerk. All abdominal reflexes were lively, and there were no pathologic reflexes. Mentally, she lay quietly in bed most of the time, cooperating with ward routine. She occasionally showed considerable irritability and emotional prodnctions. The stream of thought was entirely normal. There were no spontaneous prodnctions. There were no bizarre mental content. There were no hallucinations or delusions and no bizarre mental content. She showed no tendency to project her difficulties. Her affective

reactions were apparently adequate. There was no dissociation of affect. She showed a lively sense of humor, was actively interested in what was going on about her, being alert to even minor changes in her immediate surroundings. When not stimulated she would lie on her bed with no particular affective display. She showed no depression or spontaneous weeping. When her self-mutilation would be discussed, she would become sad, depressed and lachrymose. She showed an intense reluctance to discuss this episode. She insisted that she did not remember the details of the period during which her eyes "fell out." She clung tenaciously to this assertion for the first few weeks in the hospital. She was well aware of the seriousness of her defect. She expressed no hypochondriacal ideas. She seemed regretful regarding her misbehavior. Her memory for recent and remote events was good. Calculation and general knowledge was good. Her intelligence quotient was 82. Coöperation for mental test was entirely normal. She seemed to show good judgment and insight into everything except into the avulsion of her eyes. She admitted the other self-mutilatory tendencies and insisted that she was compelled by some peculiar force to do those "horrible things." She, however, denied that the same mental processes were responsible for the injury to her eyes. She improved rapidly both physically and mentally, and became spontaneously more cheerful, vivacious, interested in the other patients, began to coöperate, was active in the occupational therapy class and readily learned the Braille system of reading.

Careful psychologic probing was avoided because such attempts usually precipitated periods of marked dejection and apparently interfered with her progress. Analysis of dream material and association experiments yielded data of little value. Her psychosexual life was superficially uneventful. There is no record of any serious psychosexual trauma. She admits casual masturbatory activities but denies such as a regular practice. There have been no heterosexual contacts. There is no history of sexual delinquency or erethism such as one occasionally encounters in girls with chronic encephalitis. Her fantasy life is concerned mainly with details of family relations and loss of her vision. We have not probed much beyond the surface. Such investigations are being continued. There have been no self-mutilatory tendencies noted for the past 6 months. About 4 months after her admission to the Montefiore Hospital she finally admitted that she was untruthful in maintaining lack of knowledge of what happened. She admitted actually tearing out her own eyes with her fingers and ascribed this behavior to an irresistible urge. She said, "I was like hypnotized at the time, something made me do it." She never expressed any suicidal ideas. She states that she wants to live. There is no evidence of a reactive depression. The girl has made a very good adjustment in the hospital.

Early in July, 1932, she began to express mild paranoid ideas, felt the other patients were talking about her, and criticizing her. These mild ideas of reference, however, in no way changed her behavior. There has been no recurrence of self-mutilatory tendencies, affect remains normal and there are no hallucinations.

Other cases reported in the literature are reviewed and the nature of the underlying psychosis discussed.

Discussion. Self-injury by avulsion of one's eyes is rare, though known to legend in the *Œdipus* story, and the self-mutilation of the patron saint of eye diseases, Santa Lucia. There are 4 cases recorded in medical literature of patients who, in a similar fashion to our own, tore out both of their eyes, and 17 who succeeded in gouging out only 1.

We cannot include in our review reports in daily newspapers, a number of which we have noted in our search for records of such cases. Most of the cases have been described by ophthalmologists with very little comment on the psychiatric aspects of the cases, and a great many of the recorded instances are dated before the development of modern psychiatric nosology. We consequently have found it difficult at times to exactly classify the types of mental reactions in these patients.

1. Bergman, in 1846, presented the history of a widow, aged 43 years, who was always melancholy and somewhat religious. On June 21, 1836, she moaned, sighed, cried, complained of her unhappy fate, her sins and foibles. Her case was diagnosed at the time as mania religiosa. On June 28 she was found in bed, her face covered with blood and without eyes. She had not left the bed, but seemed to sleep with her bedclothes over her, and while in that position pulled out her eyes. When asked for the reason for her rash deed she referred to Matthew, Chapter v, Verse 29: "and if thine right eye causeth thee to stumble, pluck it out and cast it from thee." Her neighbors stated that for 3 years previous to her present illness she was seclusive, read a great deal and that 8 days prior to her admission she locked herself up in her own room and refused to answer any callers. She expressed religious delusions, and also entertained ideas of persecution. She made many attempts to hurt herself. An older sister suffered from a similar psychosis. The clinical picture suggests an involuntional melancholia.

2. Goffin, in 1887, reports a case of a man, aged 52 years, who was admitted to the hospital on April 11, 1887, after a night of excitement. He bade his wife and children to obey orders, made them sing together, then dance and pray, and insisted on religious poses and attitudes. Frightened by his peculiar behavior, they went to another room and locked themselves in. He soon quieted down, went to a neighboring convent and refused to leave the building, insisting that God ordered him to be there. He had to be forced and restrained and removed to the hospital. On the way he confessed and said that he was damned and unworthy of divine compassion. During the stay in the hospital he showed religious exaltation, manic excitement, irritability and stubbornness. He refused to eat and drink. The next day he showed ideas of grandeur and great wealth. On the third day he looked excited and upset and at noon of that day was asleep, and the attendant left the room. Ten minutes later an unusual noise was heard, and when the attendant entered he found the patient with the index finger of each hand in his eye and with his feet up against the bed. The lower lids were found torn in the center. The right eye was not in place and the left eye was almost out of its socket. He ascribed this act to the voice of God, who insisted that he sinned and that he tear out the eye which beheld the "nakedness" of his daughter. Rapid onset of dementia was the further course of this patient. General paresis was a very probable diagnosis in this case.

3. Szigeti merely states in a brief communication to the Thirteenth International Congress of Medicine at told him of an insane patient who tore out his eyes with his own hand. No further details are available.

4. Terson, in 1911, tells of being called to see a woman, aged 41 years, who avulsed her own eyes in the presence of a more or less sleepy attendant. The patient was depressed with religious delusions. Two centimeters of 1 optic nerve and 1.5 cm. of the other were torn.

5. Blondel quotes the record of a patient with hysteria who pulled out her own eyes. He gives no details. (We have not been able to verify this reference.)

Von Carion, Cooper, Deardon, Nettleship and Smelanskij report patients who gouged out 1 eye, but give no details regarding their mental state, except to say that they are insane or inmates of asylums. The interest in the cases apparently lay in the surgical aspects of the self-mutilation.

Despagnet's patient had delirium tremens. Adams, Cronigneau and Buchanan report depressions in women about the menopause, the last case being definitely diagnosed as involuntional melancholia. Axenfeld tells of a young woman who removed 1 eye during a "religious depression." Coggin calls the mental state of his patient, religious excitement; Wachsmuth, catatonic excitement; Idler's, Howden's and Kayser's cases strongly suggest schizophrenia.

There are a number of other cases recorded of severe injuries to the eye without complete self-enucleation. There is no essential difference from a psychopathologic standpoint between these unsuccessful attempts and the above consummated avulsions. Fulton's patient practically tore his eyeballs from their sockets during a protracted alcoholic debauch. Dehn tells of a young girl, aged 15 years, who injured her eyes so severely during an attack of manic excitement that they had to be enucleated. Chalupecky's patient, a girl, aged 18 years, apparently in a catatonic state, severely injured her left eye. One of Axenfeld's patients was a parietic who acted under a delusion that he was going to the army. Another was apparently in an acute depression cyclothymic in nature, and a third in a state strongly resembling manic depressive stupor. Lafon tells of a serious self-injury to eyes in a manic depressive, aged 40 years, with a severe reactive depression. Harries, Furst and Axenfeld record cases of dementia precox, the self-mutilatory attempts usually being in reaction to hallucinatory experiences. All the cases recorded were psychotic and in the setting of severe mental disease attempted this unusual form of self-mutilation.

In a number of instances the ophthalmic surgeons noted with some wonder the very neat enucleation of the eyeballs by the patients. Wachsmuth notes that the eye looked as though removed by operation, and Kayser says that the eye appeared as though enucleated by an expert. Von Carion, in 1859, also noted that the appearance of the eye was as if cut by a knife. The successful and complete evisceration was also noted in our own case.

A fatal suppurative meningitis was recorded by Nettleship. Surprisingly, no other similar sequel is included in the case records. Von Carion's patient apparently had a transitory infection of the sockets before complete healing. Chalupecky's and Furst's case later developed panophthalmitis. The infrequency of infection is noteworthy.

A few of the observers have recorded the lengths of the optic nerve torn with the eyeball. Buchanan reports the nerve severed close to the eyeball and Smelanskij, torn at the sclera. All the others who record the details say the optic nerve usually gave way much further posteriorly. Nettleship states that the optic nerve was torn at the commissure. MacKinlay notes that the nerve was severed so far back that no projecting portion was seen at the foramen. Various lengths of the optic nerve avulsed have been recorded by those who gave preciser details. Kayser's case had 4.5 cm. of the optic nerve, apparently to the chiasm. In our patient the left nerve was 2 inches long and the right optic nerve was 1 inch. The left optic nerve was probably torn at the chiasm. The length of the optic nerve when stretched, as given by Merkel and Kallius in the Graefe-Saemisch *Handbuch*, varies from 2.9 to 5.1 cm.

Ophthalmologists have noted that when the optic nerve is suddenly pulled at, it tears most readily at its junction with the chiasm, where it apparently is more fragile. Coppez, in 1929, experimentally proved that generalization and reported a case of anterolateral compression of the skull with avulsion of an eye and temporal hemianopsia, on the opposite side. St. Martin and Claer reported similar accidents with dislocation of the eyeball and unilateral temporal hemianopsia. Kayser's patient also showed temporal hemianopsia in the remaining eye.

The question of the possibility of rapidly enucleating an eye with the fingers was solved experimentally by Axenfeld, who, in 1899, enucleated an eye in 1 minute on a fresh cadaver. He also showed that one cannot pinch off the optic nerve and sheath with the nail and that the tearing of this nerve is probably due to a sudden pull on its fibers.

The psychopathology of self-blinding deserves comment. Blondel noted that it is not one of the rarest types of self-mutilation, and suggested the interesting term *oedipism*. There is no doubt about the fact that occasionally injury to the eyes is more or less fortuitous. In repeated attempts at self-injury, such as one frequently sees in patients with suicidal ideas, there must occasionally result injury to the exposed and relatively vulnerable eyes. Idler, Howden, Adams—all report repeated self-mutilations. Our own case bit her tongue, pulled out her teeth and scratched her face.

In other cases the attempt to injure the eyes as such has particular significance. It is interesting that in 3 of the recorded cases, those of Bergman, MacKinlay and Kayser, the patients reacted to the well-known admonition in Matthew, Chapter v, Verse 29. Many of the patients acted in response to auditory hallucinations. In these latter cases one cannot ignore the pathoplastic significance of certain psychodynamic situations which many of the psychoanalysts have emphasized. Ferenczi and Reitler have pointed out

the reality and significance of eye symbolism—the equating in the unconscious of the genitals and the eye. Self-blinding, therefore, is a form of self-castration and evidence of the operation in the subconscious of the primitive talion principle (An eye for an eye, etc.). Bryan confirms the existence of such symbol formation. Howe, in studying the problem of compulsive thinking, noted a patient who admitted “I feel I want to gouge out my eyes.” Analysis of this individual, in the opinion of the author, left no doubt as to the castration symbolism.

Abraham has clearly enumerated the varied manifestations of the castration complex in the female. Thus it may be that in a certain proportion of patients acutely psychotic, these deeply lying unconscious complexes may come to the surface and, uninhibited, discharge along these unusual channels. Stern has shown how masochism can be brought about by the encephalitic process. Jelliffe, in his well-known effort to clarify psychosomatic relations, has shown how encephalitis can bring about “regression or dissolution of function to earlier stages of organization.” Lewis points out how a castration complex can be brought to the surface by the paretic process. We must admit that in this case, because of continued lack of coöperation of the patient, we have not been able to trace in desired detail the psychodynamic significance of the self-blinding.

We have been able to find only 2 cases on record of self-mutilation of teeth. One, in a patient reported by Allaman in 1913, was apparently a case of dementia precox and he pulled his own teeth in reaction to various delusions. In 1927 Claude, Baruk and Lamache reported a young man, aged 22 years, with chronic encephalitis, who among other compulsions pulled 12 of his own teeth. There are many records in the anthropologic literature of so-called ethnic mutilations (Deniker), where in various social groups in Africa, North America, etc., there exist rather painful self-mutilatory processes dictated by the *mores* within the particular group. Julian Huxley noted while traveling through Africa, in 1931, “they extract their own teeth and then take those of animals, file the ends and screw them into the vacant sockets.” There are many other similar observations.

Allaman's patient used a dental forceps which he stole from the asylum cabinet. No mention is made of instrumentation in Claude's case. Our patient used her fingers. One is almost tempted to assume that the teeth were loosened in their sockets to permit such facile extraction. We have noted in our experience unusually rapid decay and loosening of teeth in patients with chronic encephalitis, who are usually very young individuals. More careful study of this problem is needed. Mori definitely notes an increase in the amount of caries in the teeth of a patient with chronic encephalitis and attributes these changes to involvement

of the fifth nerve which controls the trophic influences going to the teeth.

Our patient is the only one in this literature on self-blinding with chronic encephalitis. The self-mutilatory tendencies noted in her we consider as compulsion phenomena. Compulsions have been rather frequently described in chronic encephalitis: Compulsive shouting, by Benedek and Shuster; sudden desire to break things in a patient of Claude and Tinel and Michon; homicidal and suicidal tendencies of obsessive nature in the case of Pascal, Vié and Agasse; impulse to strangle wife and child in Laignel-Lavastine and Desoille's patient; compulsive thinking in the case of Stern's patient during oculogyric crises. In our own practice we have frequently encountered such compulsive tendencies of diverse nature. Much of the antisocial behavior partakes of this character.

The rarity of compulsions to self-mutilation in encephalitis is striking. Conn recently reported such an instance with a history of fracturing a number of her bones. Claude and his coworker's case has already been referred to.

The repeated insistence of this patient during her early illness of complete amnesia for the period of self-injury brings up the question of the incidence of such confusional states in chronic encephalitis. They certainly are rare. One must be very careful in evaluating the patient's statements regarding such loss of memory for the details, especially of criminal behavior. Sittig reports a patient with an alleged amnesia for a sexual assault in a chronic encephalitic, aged twenty-one years. He indicates that he thought the patient was lying and simulating. In our own patient, after a few months of repeated attempts to obtain the truth, the patient finally admitted that she deliberately lied and that she recalled the process of self-mutilation. Boenhoffer notes the rarity of amnesia for acute episodes in encephalitis, stating that he never encountered any in 200 cases. Briand, Gelma, Meyer and Rossi, however, report patients with amnesia for antisocial conduct. One must accede that rarely such transitory confusional states with amnesia may occur, though one must conserve considerable scepticism for each particular case.

Examination of this patient very soon after the avulsion showed no sensory anomalies. She admitted slight pain during the process of self-injury. One must assume a transitory affection of the pain perception mechanism, perhaps that one described by Schilder and Stengel in the supramarginal gyrus. That analgesias occur during states of intense emotion is well known. This irresistible impulse must have been accompanied by a powerful effect. The patient recalls a transitory state of lively anxiety, but cannot accurately describe her state of mind at that time. Courbon reports an interesting case of a mentally defective woman who, though repeatedly mutilating herself with apparent analgesia, showed marked

hyperalgesia when any attempt was made to treat or examine her. This shows the marked effect of representations and ideas in suspending and modifying the activity of the pain perception centers. Transitory analgesias are not unknown in the psychoses though their explanation is still unsatisfactory (Bleuler). One of us saw a transitory universal analgesia lasting 3 days in a perfectly wide awake paranoid schizophrenic. Analgesias occurring in patients with depression and with nihilistic ideas were mentioned many years ago by Cotard. In some way the encephalitic process affected the pain perception mechanism so that its activity was suspended for a brief interval during which time this remarkable self-injury took place. The rôle in this ease of self-puncture, masochistic or other subconscious determinants needs further study.

Summary.—A young girl, aged 16 years, with chronic encephalitis, suddenly gouged out both her eyes while under observation in a general hospital. During a period of about 2 years she pulled out all but 7 of her own teeth.

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THE DIGESTION OF PROTEIN BY PATIENTS WITH GASTRIC ANACIDITY.

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SINCE the introduction of histamin as a stimulus to gastric secretion, it has been demonstrated that the juice from some stomachs contains not only no free hydrochloric acid but also very little pepsin.¹⁷ It would seem of interest to inquire whether such profound changes in gastric secretion are followed by alterations in digestion.

Two questions present themselves in such an inquiry: (1) Is digestion normally complete in patients with gastric anacidity? and (2) is digestion faster or slower than normal in such patients? Discussions of these questions constitute the two parts of the present paper. In both, consideration is limited to protein, since it is the only foodstuff on which the action of gastric juice is important.

PART I. COMPLETENESS OF DIGESTION.

Since protein which is not digested is not absorbed in appreciable amount, it must be excreted in the feces. Fecal nitrogen may then

become an index of protein digestion. For it to be a valid index under all conditions, a further assumption would be necessary: Namely, that no protein which has been digested remains unabsorbed to be excreted in the feces. Our results, however, are such as to render this assumption unnecessary in the present instance. We have therefore chosen fecal nitrogen as our index of the completeness of protein digestion.

Literature. The early literature on human fecal nitrogen in health was summarized by Thomas in 1909.²² He found that in unselected cases on the average human diet the fecal nitrogen might be 2.6 gm. or more daily. The average was 1.0 to 1.5, and the lowest was 0.7 gm. daily.

A number of workers have concluded that in man and animals the nitrogen content of the feces is dependent largely on the bulk of the food residues, the nitrogen of the diet, provided it be digestible, having little effect.^{12,14,15} Corroborative evidence for this conclusion is found in the data of Sehamberg *et al.*¹⁹ from their work on the effect of diet in psoriasis. Their figures for 7 patients are taken, covering a total period of 368 days.

Of these patients 5 had no history of gastrointestinal disease, 1 had had a single attack of jaundice, and 1 had had several attacks of jaundice and was subject to bilious attacks. Gastric analyses were not reported. The periods for each diet and stool collection usually covered a week.

The nitrogen in the diet ranged from 0.5 to 38.6 gm. daily, the fecal nitrogen from 0.54 to 2.66. The mean nitrogen in the diet was 13.75 ± 0.82 gm., with a standard deviation of 8.75 ± 0.58 gm. The mean nitrogen in the stool was 1.36 ± 0.045 gm., with a standard deviation of 0.48 ± 0.032 gm. The correlation coefficient between dietary and fecal nitrogen is 0.236 ± 0.088 , and the correlation ratio is not significantly different from this. These figures indicate no significant association of dietary and fecal nitrogen in this group of patients unselected from the point of view of gastrointestinal disease.

Investigating patients with no free acid following the Ewald meal, von Noorden,²³ Strauss,^{20,21} and Mayer¹³ determined the fecal nitrogen after known diets. They found an increase only in the presence of diarrhea. The results are, however, not significant with respect to the digestion of protein in anaemia except in the cases of pernicious anemia, since it has been demonstrated many times in the last few years that people who fail to secrete free acid after a meal of bread, gruel, or even alcohol may have a normal acidity during more powerful stimulation, such as from histamin or from meat.¹⁸

Material. The patients used in the present studies were selected on the basis of availability from the "anaemia clinic."¹⁶ They belong, with the possible exception of Case 2, to the group of

"unexplained anaacidities,"¹⁶ a group in whom the anaacidity is not associated with anemia or demonstrable gastrointestinal disease. All had had repeated tests of gastric secretion which in each case yielded only a few cubic centimeters of neutral mucus even after the powerful stimulus of histamin.

Clinical Summaries. CASE 1.—C. E., male, aged 68 years, caretaker, had a carcinoma of the lip removed in 1928 without recurrence to date. His present diagnosis is arteriosclerosis and gastric anaacidity, the latter discovered accidentally in April, 1930, during a routine hospital workup. He has no gastrointestinal complaints, has never been anemic, and repeated gastrointestinal roentgenograms have been negative. The urine is normal, and there are no signs of kidney disease.

CASE 2.—G. F., male, aged 47 years, road-crew boss, had chronic arthritis of spine and chronic iritis (both inactive at present), polyposis of stomach, and anaacidity. The urine is negative, and there is nothing to suggest kidney disease. The anaacidity was discovered accidentally in 1929. Roentgenograms were taken in June, 1930, as part of the routine of the anaacidity clinic, and there was reported a "pyloric zone widened by an irregular filling defect on the greater curvature. This was perfectly definite and constant." In December, 1931, "there was seen on the films and fluoroscopically a wide irregular pyloric zone which could not be pressed into a normal-looking structure. The films show what appears to be a string of polyps throughout the prepyloric antrum." The patient is clinically well and is working. He has no gastrointestinal symptoms and no anemia. He refuses operation.

TABLE 1.—DAILY NITROGEN EXCHANGE IN PART I.

	Fasting Bl. urica, mg. per 100 cc. Bl.	Diet, N in gm.	Urine, N in gm.	Stool, N in gm.
CASE 1.				
Day 1	39.0	20.1	12.8	{ 1.1
Day 2	20.1	16.0	{ 1.1
Day 3	20.1	16.0	{ 1.1
	42.0			
Day 4	1.3	13.6	{ 1.3
Day 5	1.3	6.2	{ 1.3
Day 6	1.5	5.4	{ 1.3
	31.5			
CASE 2.				
Day 1	36.0	20.1	13.7	{ 1.6
Day 2	20.1	18.1	{ 1.6
Day 3	20.1	19.3	{ 1.6
	25.5			
Day 4	1.3	11.5	{ 1.6
Day 5	1.3	6.7	{ 1.6
Day 6	1.5	5.0	{ 1.6
	22.5			

Methods. The experimental procedure had as its purpose the comparison of fecal nitrogen during periods of high and of low nitrogen ingestion. A low-nitrogen diet was prepared consisting of vegetables, fruit, fruit juices, carbohydrate, and fat, with a daily caloric value of about 1900 and a daily nitrogen content calculated as less than 1.5 gm. To make a high-nitrogen diet of the same bulk, enough meat was added to bring the daily nitrogen to 20 gm., and

enough fat and concentrated carbohydrate were omitted to keep the total caloric value unchanged. Each diet was fed for a 3-day period, the high-nitrogen first. Fluids were kept at about 2.2 liters per day. The nitrogen content of the diet was calculated from tables^{3,11} and is only approximate.

On these diets the urine and stool were analyzed for total nitrogen, the urine being collected for 24-hour periods, the stool for each 3-day period with capsules of carmine as markers. The stools were transferred to strong sulphuric acid immediately after collection and were later digested until reduced to a uniform thin suspension from which samples could be pipetted into Kjeldahl flasks.

Results. All the stools were well-formed and normal in appearance. The fecal nitrogen, recorded in Table 1, is in all cases within the normal range and shows no significant difference between the period of high- and of low-nitrogen intake.

Summary and Conclusions of Part I. 1. In studying the digestion of protein in 2 patients with gastric anacidity, the fecal nitrogen was determined.

2. No significant change or deviation from normal was found after high- and low-nitrogen diets of equal bulk.

3. It is therefore concluded that in such patients the digestion of protein may be normally complete.

PART II. RAPIDITY OF DIGESTION.

The simplest way of measuring the rapidity of protein digestion would be through direct examination of the intestinal contents as digestion is completed. This is obviously impossible in man, and one is forced to employ a more indirect method. For the present study we have taken as an index of the rapidity of protein digestion the rate of nitrogen excretion in the urine following a high-protein meal in a patient already in nitrogen equilibrium at a high level.

Before the nitrogen of ingested protein can make its appearance in the urine the protein must be digested, absorbed, transported to the liver, deaminized, and the nitrogen carried to the kidneys and excreted. Thus for urinary nitrogen to be an index of protein digestion there must be no departure from normal of the intermediary processes.

If after protein ingestion, however, nitrogen should appear in the urine as promptly and adequately in patients with anacidity as in normals, one would seem justified in concluding that not only digestion but also absorption and the intermediary processes were normal. With prompt excretion of nitrogen in patients with anacidity, to postulate delayed digestion would necessitate assuming equally accelerated intermediary metabolism, a condition not only highly unlikely but forming, if in several patients, a series of very rare coincidences.

Literature. To test the rate of digestion, absorption, and metabolism of protein, Gruber⁷ fed meat to fasting dogs and found that nitrogen elimination began promptly, reached its maximum in 5 to 7 hours, and subsided in 12 to 24 hours. Increasing the amount of meat or adding fat delayed the maximum. Firgau⁵ in a similar procedure found that adding carbohydrate had no effect. Janney⁹ found the same curve of nitrogen elimination in dogs made diabetic by phlorhizin. He also found¹⁰ that the glucose derived from the protein was excreted almost as rapidly as the nitrogen.

In man Haas⁸ found two maxima of urinary nitrogen, one in the second hour, and one in the fifth. As a mixed meal was administered in each case, the results are difficult to interpret.

Material. The patients used belong to the same group as those employed in Part I. Clinical summaries follow:

CASE 3.—A. J. G., male, aged 65 years, retired sheriff-keeper, had hypertension, general arteriosclerosis, renal arteriosclerosis, spondylitis deformans, glaucoma, ventral hernia, gastric anacidity, and psychoneurosis. In spite of the lengthy diagnosis he leads a normal life. His only complaint is of epigastric fullness after eating or drinking small amounts. It is interesting that in connection with other experiments⁴ he swallowed a balloon which was inflated in his stomach to 1500 cc. without causing distress. His anacidity has been known since 1925. He has never been anemic, and repeated gastrointestinal roentgenograms have been negative.

The urine contains a faint trace of albumin, but a fasting blood urea was 37.5 mg. per 100 cc. blood, the phthalein excretion was 50 per cent in 2 hours, and the Addis ratio² showed 70.5 per cent of normal kidney tissue, an insignificant impairment.

CASE 4.—C. O., male, aged 64 years, laborer, had indigestion and gastric anacidity. Although he complains of constipation and a constant feeling of epigastric fullness for many years, he has gained 15 pounds in the past 5 years. He is in excellent health, is not anemic, and gastrointestinal roentgenograms have been negative. The urine is negative, and there is nothing to suggest kidney disease.

CASE 5.—I. P., male, aged 62 years, salesman, had gastric anacidity, and syphilis (Wassermann, treated). His eating habits have always been poor, and in 1903 he began to have epigastric distress after meals. A doctor passed a stomach tube at that time and told him he had "catarrh of the stomach." In 1916 he was told at the Mayo Clinic that he needed hydrochloric acid. He appeared at the Stanford Out-patient Department in 1922 with the same complaint of indigestion. At that time there was no acid after the Ewald meal, but gastrointestinal roentgenograms were negative and there was no anemia. His status has not changed since then, except that the histamin test has revealed his anacidity as a true one. While in the hospital for the purpose of this study his gastrointestinal symptoms disappeared entirely, to reappear a week after dismissal. The urine is negative, and there is nothing to suggest kidney disease.

CASE 6.—T. M., female, married, aged 26 years, apartment-house manager, had rheumatic heart disease (inactive), cardiac dilatation and hypertrophy, mitral stenosis and insufficiency, gastric anacidity, and psychoneurosis. Compensation is excellent. She complains of anorexia and epigastric distress, with belching and fullness after meals. Her weight has, however, been constant, there is no anemia, and repeated gastrointestinal roentgenograms have been negative. The urine is negative, and there are no signs of kidney disease. Her anacidity was discovered in 1930.

As controls, 3 healthy hospital house officers with normal gastric secretions were used. They will be designated by their initials to distinguish them from the patients.

Methods. The immediate object of the experiment was to determine the nitrogen content of the urine at frequent intervals after the ingestion of a single large quantity of protein. The protein was given in the form of a breakfast of beefsteak after an overnight fast. The patient was encouraged to eat as much beefsteak as possible. He received no other food until evening, when he was given a 1000-caloric supper containing less than 1 gm. of protein (0.16 gm. nitrogen). Fluids were kept at a total of about 2 liters distributed through the day.

The beefsteak was in some instances ground before cooking. The patient was then allowed to eat it normally, with chewing. In other instances the beefsteak was cooked whole and then cut into half-centimeter cubes which were swallowed without chewing.

To insure nitrogen equilibrium before the experiment, the patient was placed for the first 3 to 5 days on a control diet of 1.5 times the patient's calculated basal caloric requirement (reduced by 100 calories for hospital patients) containing 1.2 gm. of protein per kilogram of body weight. In 1 case the control diet was resumed for a day following the beefsteak day.

During the beefsteak day and the day immediately preceding it, the urine was collected every 2 hours during the day, with an 8-hour interval at night. On the other days 24-hour specimens were kept. The stool was collected from some of the patients. Urine and stool were analyzed for nitrogen by the Kjeldahl method, and the urine was also analyzed for urea by the method of Addis.¹

Urea rather than total nitrogen of the urine was taken as the measure of protein absorption, because urea, being the direct end-product of deamination of protein, would be expected to reflect more delicately in its excretion any changes in protein absorption. Confirmation of this reasoning is found in Table 3 in the fluctuation of the figures for urea nitrogen with change of diet, as contrasted with the relative constancy of those for "total nitrogen less urea nitrogen" (column 4).

Results. The results are detailed in Tables 2, 3 and 4. The data of Table 2 are shown graphically in Figs. 1 and 2. In each graph the actual length of the unit in each ordinate scale has been made proportional to the total quantity of beefsteak eaten; so that the same actual height of ordinate during the beefsteak day in any 2 cases represents an excretion of the same proportion of the ingested nitrogen. Thus the curves for the beefsteak days are directly comparable to one another in terms of relative proportions of ingested beefsteak excreted as urea.

It will be noted from Table 3 that in each patient the urinary nitrogen was practically constant for at least 2 days preceding the

TABLE 2.—UREA EXCRETION IN GRAMS UREA NITROGEN PER HOUR IN PART II.

N in diet 24-hr. total	D. C. H. Ground beefsteak.		D. C. H. Cubes of beefsteak.		A. H. Cubes of beefsteak.		J. P. S. Cubes of beefsteak.		Case 3. Ground beefsteak.		Case 4. Ground beefsteak.		Case 4. Cubes of beefsteak.		Case 5. Cubes of beefsteak.		Case 6. Ground beefsteak.	
	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.	Control.	Beefsteak.
12 00	20.00	12.00	11.00	14.40	14.00	12.80	32.80	9.30	17.00	9.10	13.40	9.10	17.60	11.50	20.00	10.60	12.80	
24-hr. total	12 10	17.82	11.16	11.04	12.00	13.12	12.96	6.50	10.92	9.76	10.94	9.70	10.92	8.62	11.46	7.14	9.22	
7 to 9 A.M.	0.52	0.48	0.45	0.45	0.35	0.42	0.62	0.22	0.23	0.15	0.10	0.47	0.41	0.26	0.53	0.37	0.28	
9 to 11 A.M.	0.47	0.74	0.50	0.58	0.56	0.65	0.54	0.33	0.65	0.47	0.67	0.57	0.48	0.28	0.36	0.38	0.55	
11 A.M. to 1 P.M.	0.51	1.02	0.56	0.63	0.46	0.70	0.50	0.31	0.57	0.42	0.14	0.56	0.49	0.38	0.39	0.31	0.49	
1 to 3 P.M.	0.43	1.28	0.48	0.68	0.38	0.65	0.59	0.81	0.29	0.42	0.83	0.46	0.47	0.38	0.59	0.34	0.34	
3 to 5 P.M.	0.61	1.12	0.57	0.60	0.42	0.64	0.70	0.34	0.68	0.48	0.67	0.40	0.50	0.42	0.56	0.38	0.47	
5 to 7 P.M.	0.52	0.84	0.52	0.55	0.53	0.60	0.35	0.29	0.56	0.39	0.62	0.35	0.69	0.46	0.42	0.35	0.53	
7 to 9 P.M.	0.64	0.96	0.52	0.55	0.51	0.62	0.66	0.36	0.61	0.60	0.56	0.45	0.62	0.42	0.49	0.36	0.46	
9 to 11 P.M.	0.67	0.79	0.54	0.44	0.63	0.60	0.68	0.15	0.43	0.51	0.88	0.35	0.40	0.47	0.55	0.36	0.53	
11 P.M. to 7 A.M.	0.42	0.42	0.36	0.26	0.54	0.42	0.46	0.24	0.26	0.36	0.25	0.31	0.35	0.31	0.46	0.18	0.24	
Steak at:	8 to 8.52 A.M.	7.55 to 9.20 A.M.	7.50 to 9 A.M.	10.30 to 10.50 A.M.	8 to 9 A.M.	7.20 to 7.40 A.M.	7.17 to 8.15 A.M.	7.15 to 9.30 A.M.	8 to 9 A.M.	7.20 to 7.40 A.M.	7.17 to 8.15 A.M.	7.15 to 9.30 A.M.	8 to 8.50 A.M.					

TABLE 3.—NITROGEN EXCHANGE IN PART II.

Diet.	Grams N in diet, calculated.	Total N in urine, gm.	Urea N in urine, gm.	Total N less urea N.	N in stool, gm.
Normal Control D. C. H.					
Day 1—Control	12.0	13.0			
Day 2—Control	12.0	14.8			
Day 3—Control	12.0	14.2	12.1	2.1	
Day 4—500 gm. finely ground beefsteak	20.0	20.0	17.8	2.2	
Normal Control D. C. H.					
Day 1—Control	12.0	13.1	{ 0.8
Day 2—Control	12.0	13.3	11.2	2.1	
Day 3—275 gm. beefsteak in cubes	11.0	13.0	11.0	2.0	
Normal Control A. H.					
Day 1—Control	14.4	13.4			
Day 2—Control	14.4	13.7			
Day 3—Control	14.4	14.7	12.0	2.7	
Day 4—350 gm. beefsteak in cubes	14.0	15.8	13.1	2.7	
Normal Control J. P. S.					
Day 1—Control	12.8	14.3	{ 2.1
Day 2—Control	12.8	13.4	
Day 3—Control	12.8	15.4	13.0	2.4	
Day 4—Control diet plus 500 gm. beefsteak in cubes	32.8	20.3	17.4	2.9	
Case 3.					
Day 1—Control	9.3	7.3			
Day 2—Control	9.3	7.1			
Day 3—Control	9.3	7.4	6.5	0.9	
Day 4—425 gm. finely ground beefsteak	17.0	12.2	10.9	1.3	
Case 4.					
Day 1—Control	9.1	10.9			
Day 2—Control	9.1	10.3			
Day 3—Control	9.1	11.7	9.8	1.9	{ 2.0
Day 4—336 gm. finely ground beefsteak	13.4	13.0	10.9	2.1	
Day 5—Control	9.1	10.6			2.7
Case 4.					
Day 1—Control	9.1	{ 2.9
Day 2—Control	9.1	
Day 3—Control	9.1	
Day 4—Control	9.1	12.0	9.7	2.3	
Day 5—440 gm. beefsteak in cubes	17.6	13.5	10.9	2.6	
Day 6—Control	9.1	12.3			7.3*
Case 5.					
Day 1—Control	11.5	{ 2.6
Day 2—Control	11.5	10.7	
Day 3—Control	11.5	10.8	
Day 4—Control	11.5	10.3	8.6	1.7	
Day 5—500 gm. beefsteak in cubes	20.0	13.9	11.4	2.5	
Case 6.					
Day 1—Control	10.6	7.5	{ 1.1
Day 2—Control	10.6	9.2	
Day 3—Control	10.6	9.4	7.5	1.9	
Day 4—Control	10.6	8.3	7.1	1.2	
Day 5—321 gm. finely ground beefsteak	12.8	10.2	9.2	1.0	

* Diarrhea.

NOTE.—The brackets in the last column indicate single periods of stool collection.

meat meal, thus assuring nitrogen equilibrium. Uniform discrepancies between total daily intake and output are doubtless due to error in calculating the diet. None of the patients gained or lost appreciably in weight.

The curves in the normals follow closely those of previous investigators, with a more or less regular rise to a maximum in about 6 hours, then a gradual fall. The excretion was as prompt and complete after cubes of beefsteak swallowed whole as after ground beefsteak well chewed. In no case was there diarrhea. These

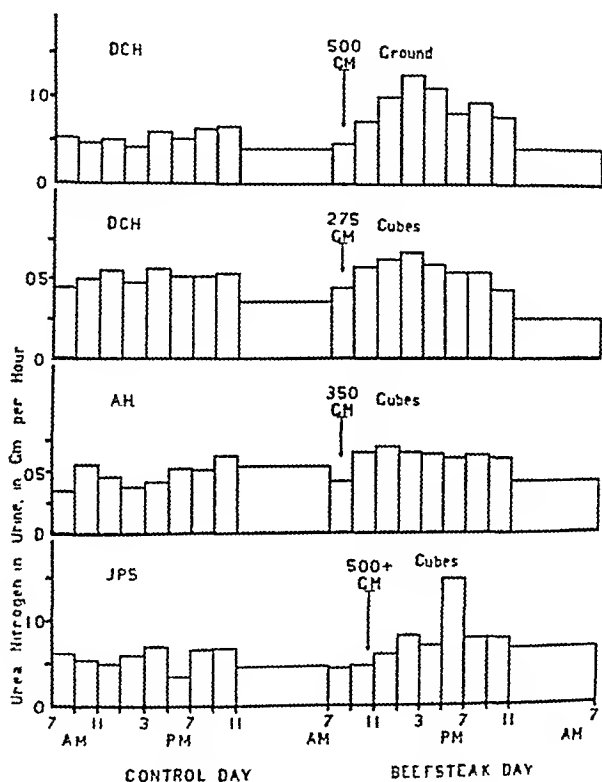


FIG. 1.—Urea excretion in normals in Part II.

results confirm those of Foster and Hawk⁶ that in normals bolted meat is practically as well utilized as overmasticated.

All the patients after ingestion of ground meat show a curve of urea excretion which is essentially normal. The low excretion between 11 A.M. and 1 P.M. of the beefsteak day in Case 4 after ground meat was probably due to loss of part of the specimen. The urine volume for the period in question was very low (70 cc. as opposed to 280 and 325 for the preceding and succeeding periods), but with almost the same urea concentration as in adjacent periods. As corroborative evidence for a loss of specimen, the total excretion

for that day shows a smaller increment than does the nitrogen ingestion.

Cases 4 and 5 after the meat cubes had diarrhea, with several loose but not foul stools. In Case 4 the diarrhea began about 12 hours after the meal, in Case 5 about 5 hours after. In neither case was there fever, cramps, malaise, or other symptom of enteritis. The low urinary nitrogen output is, of course, due to the large loss in the stools.

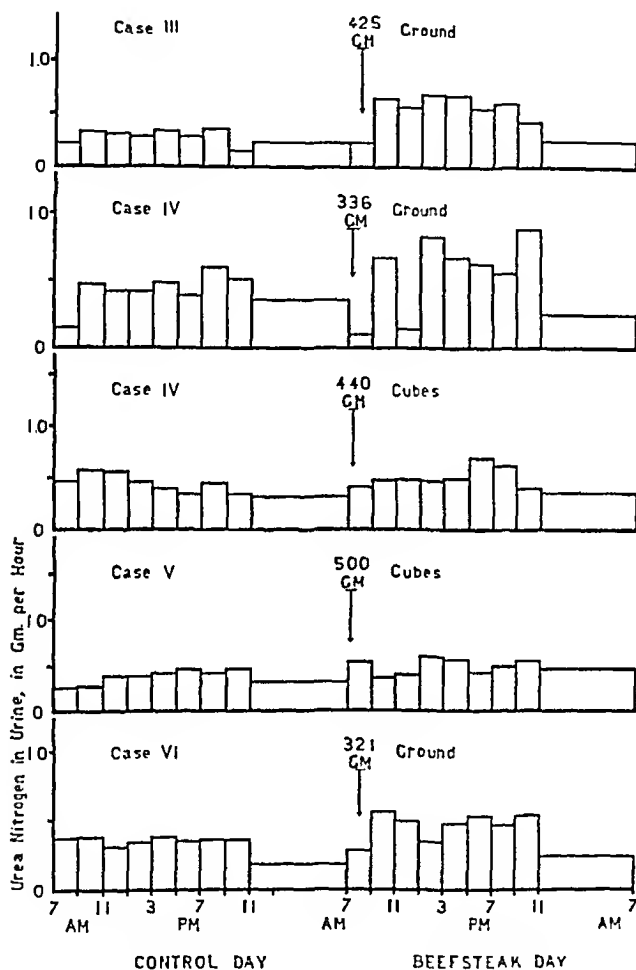


FIG. 2.—Urea excretion in patients with anacidity in Part II.

In each case, normal and anacidity, undigested muscle fibers were found microscopically in the feces from the meat meal, and there seemed to be no difference between the groups as to relative numbers of fibers or degree of digestion. In only one of the cases of diarrhea could gross meat residues be detected.

Table 4, concerning the fluid exchange, is included to complete the data.

Amount in Litens per Day in Part II.

D. C. II. Ground beefsteak.		D. C. II. Cubes of beefsteak.		A. H. Cubes of beefsteak.		J. P. S. Cubes of beefsteak.		Case 3. Ground beefsteak.		Case 4. Ground beefsteak.		Case 4. Cubes of beefsteak.		Case 5. Cubes of beefsteak.		Case 6. Ground beefsteak.	
Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.	Intake.	Output.
2	1.86	2.00	3.32	2.0	2.26	2.0	2.55	2.0	2.55
2	2.67	1.8	1.61	2.00	3.09	2.0	2.80	2.00	1.39	2.15	2.44	2.0	2.54	2.0	2.54
2	2.64	2.0	2.13	2.00	3.18	2.0	2.60	2.00	1.55	2.10	2.20	2.12	2.12	2.0	1.90	2.0	1.90
2	2.68	2.0	3.28	2.05	2.47	1.8	2.59	2.17	2.14	0.92	0.92	1.97	1.97	2.0	2.48	1.8	2.03
..	2.02	2.02	2.08	2.08

Summary and Conclusions of Part II. 1. As an index of the rate of protein digestion in patients with gastric anacidity the rate of urea excretion in the urine was determined after the ingestion of a single meal high in protein.

2. In 3 patients whose meal consisted of ground beefsteak, normal rates of urea excretion were found.

3. In 2 patients who swallowed the beefsteak in pieces without chewing, diarrhea developed with a large loss of nitrogen in the stools.

4. It is concluded that in the absence of diarrhea, the digestion of protein in patients with gastric anacidity may be normally rapid.

5. The conclusions from Parts I and II give the obvious explanation for the fact that persons with gastric anacidity may be well nourished over long periods.

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A NEW THERAPY OF PEPTIC ULCER: CONTINUOUS ALKALINIZED MILK DRIP INTO THE STOMACH.*

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THE treatment of a disease is most rational when it is based on a complete knowledge of its etiology and pathogenesis. In the case

* Read before the American Gastro-enterological Association, May 2, 1932.

of peptic ulcer (the term "peptic ulcer" will be used as referring to ulcer of the stomach, duodenum and jejunum) such an ideal state does not exist. Because of striking differences of opinion, various therapeutic methods, medical and surgical, have arisen, but none is entirely satisfactory. In proposing another therapy, it is necessary to discuss the factors which seem to play the most important rôle in the ulcer problem. It is evident that the following are prominent: (1) Excessive irritation of the mucous membrane by certain types of exogenous mechanical, chemical and thermal stimuli; (2) the chemistry of the gastric secretion; (3) the tissue response to the above factors; (4) conditions causing or, at least, initiating recurrences; (5) an "X" factor.

Given, for example, an individual, often of a certain morphologic type, in a family predisposed to the ulcer disease, with faulty dietetic habits, with tissues which react unfavorably to exogenous traumas, with a labile vegetative nervous system which initiates and exaggerates the unfavorable tissue responses, with a stomach which secretes an eroding gastric juice; and particularly given an individual who is exposed to mental, emotional and physical strains, and who reacts unfavorably to them, it would, I think, be generally accepted that we have most of the conditions entering into the problem of chronic recurrent peptic ulcer in man.

In brief, it is doubtful if there is a single definite cause of peptic ulcer. Nevertheless, despite the multiplicity and complexity of the factors just enumerated, one stands out prominently, namely, what may be termed the acid factor. A complete discussion of the rôle of gastric acidity in the pathogenesis of ulcer will not be attempted here. The following features, however, demand consideration: (1) Using histamin and neutral red to check up the supposedly anacid cases of ulcer, we have not encountered a single instance of peptic ulcer, proved at operation, without free hydrochloric acid in the gastric contents. (2) We have not seen a recurrent ulcer after subtotal gastrectomy for ulcer in a patient without free hydrochloric acid postoperatively. (3) The experiments of Mann, Exalto and Ivy, where the stomach was anastomosed with the jejunum and a duodeno-ileostomy performed, thus side-tracking the alkaline duodenal contents, with subsequent jejunal ulcer, are significant. (4) Finally it seems evident that those procedures, whether medical, as in the Sippy cure, or surgical, as in partial gastrectomy, which produce decreased or absent free hydrochloric acid, yield the best results in the treatment of peptic ulcer.

Exactly how acid participates in the ulcer problem is as yet unsolved. Does it first produce a specific ulcerative gastritis (Konjetzny, Puhl, Buchner) which, plus spastic and mechanical factors, leads to ulcer? Is it a primary hypersecretion dependent on humoral stimuli or, what is more probable, on hypertonus of the vagus nerve? Is the hypersecretion after all secondary to the lesion? Or

rather, are protecting factors against peptic digestion or acid irritation, for instance, mucin, decreased or absent? Whatever rôle one assigns to the acidity in the pathogenesis of ulcer, it should be readily admitted that its importance in relation to therapy may be strongly emphasized. One is tempted to propose as axiomatic that whatever measures will produce a harmless chronic achlorhydria will benefit peptic ulcer. This, however, is not a simple task.

The human stomach is provided with a complex neuro-humoral mechanism for the production of free hydrochloric acid which is difficult to suppress without harm to the patient. The difficulty lies in the fact that it is impossible, medically, to inhibit the chemical or humoral gastric mechanism. Surgically, true or false achlorhydria (either is apparently sufficient to prevent ulcer recurrences) has been most successfully accomplished in partial gastrectomy for gastric ulcer—here one meets practically invariably with postoperative achlorhydria.

When we consider the magnitude of the operation for the cure of peptic ulcer, we hesitate to advocate surgical therapy for every chronic ulcer. Certainly a fair percentage of ulcers, as evidenced clinically, radiologically, and from postmortem experience, heal and remain healed with (or even without) adequate medical therapy. It is, therefore, only fair, particularly where the duration is short, where the psychic and dietetic habits are good, and where the hereditary or morphologic makeup is not too pronounced, and where there are no complications, to advise medical therapy. We agree that all the factors should be considered and the following are essential in a good medical therapy: (1) Mental and physical rest; (2) mental sedatives and muscle antispasmodics; (3) local heat; (4) intestinal treatment; (5) avoidance of alcohol and tobacco; (6) eradication of reflex or other sources of irritation.

But we are chiefly concerned with the acid factor, the importance of which we have already stressed. We have pointed out some of its relations to the pathogenesis of ulcer. It is now necessary to present additional data which also lead to our therapeutic attack.

We have been impressed by the important rôle of the nervous system (vagus nerve) in the hyperchlorhydria of ulcer patients. The familiar production of acidity or ulcer symptoms by psychic traumas; the large amount of fasting and continuous secretion in ulcer patients; the high acid curves produced in ulcer patients with sham or psychic feeding (Chart I)—all attest to the fact that the nervous stimuli are excessive in ulcer patients.

Furthermore, as contrasted with controls, the patients with gastric or duodenal ulcer have a high nocturnal curve of acidity (Charts II, III, IV, V). Because of this observation one questions whether any method of medical ulcer therapy thus far advocated accomplishes what seems the logical and desirable state, namely, the institution of a chronic achlorhydria. Now what I mean by a

chronic achlorhydria is nothing more or less than a constant neutralization of free hydrochloric acid in the stomach throughout the 24 hours of the day. The Sippy treatment, in which Sippy by the use of cream and milk hourly, 12 hours daily, alkalies and evening aspirations, strove to establish a constant anaecidity, does not realize that ambition. (In fact, our studies showing the high night acidity curves were made with the ulcer patient on Sippy régime.)

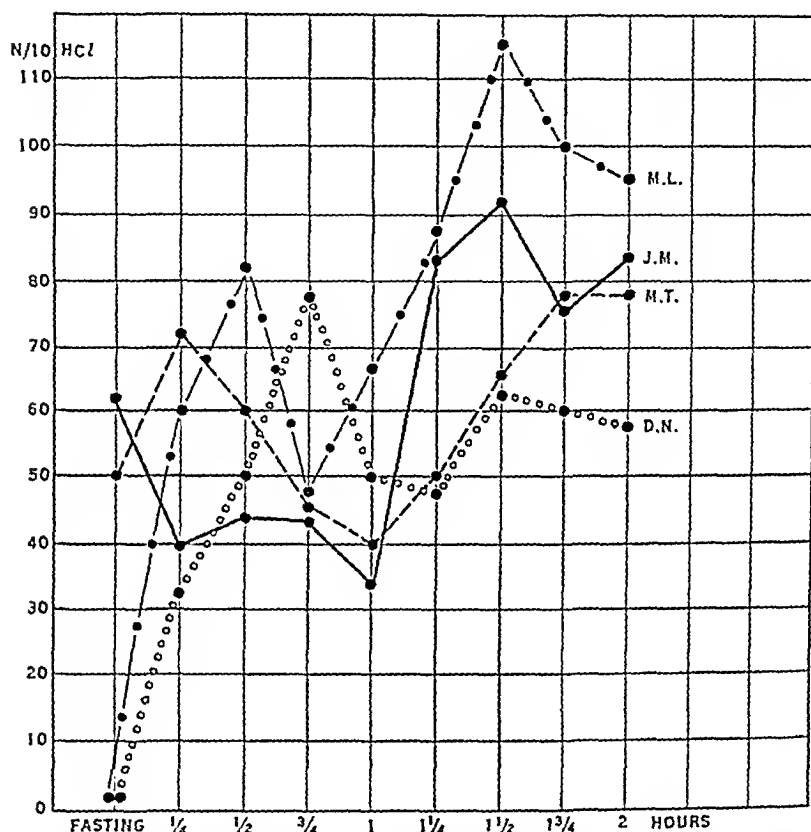


CHART I.—Sham feeding (vagus) curves of free hydrochloric acid in duodenal ulcer cases. In this test, adult male patients swallow the Rehfuß tube in the fasting state, then an orange is chewed but not swallowed.

Because of all the foregoing considerations, and, for other reasons to be mentioned later, the following plan of attack on the acid factor in the treatment of peptic ulcer was formulated.

Method. A Rehfuß tube is passed into the stomach of the patient and connected by a fairly long piece of rubber tubing to a gravity flask, and a Murphy drip indicator is interposed in the system. A solution consisting of milk containing 5 gm. of bicarbonate of soda to the quart is allowed to drip into the stomach at the rate

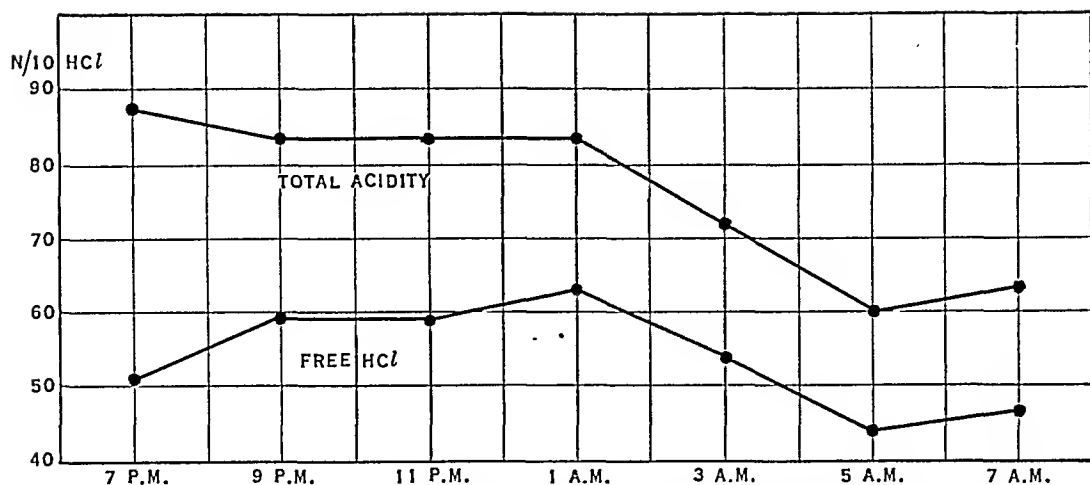


CHART II.—Night Rehfuß test—composite curve in 25 duodenal ulcer cases. Adult male patients eat a mixed meal at 5 P.M. At 7 P.M. the Rehfuß tube is swallowed and a sample aspirated every 2 hours during the night. The patient fasts, and as a rule, sleeps through the night.

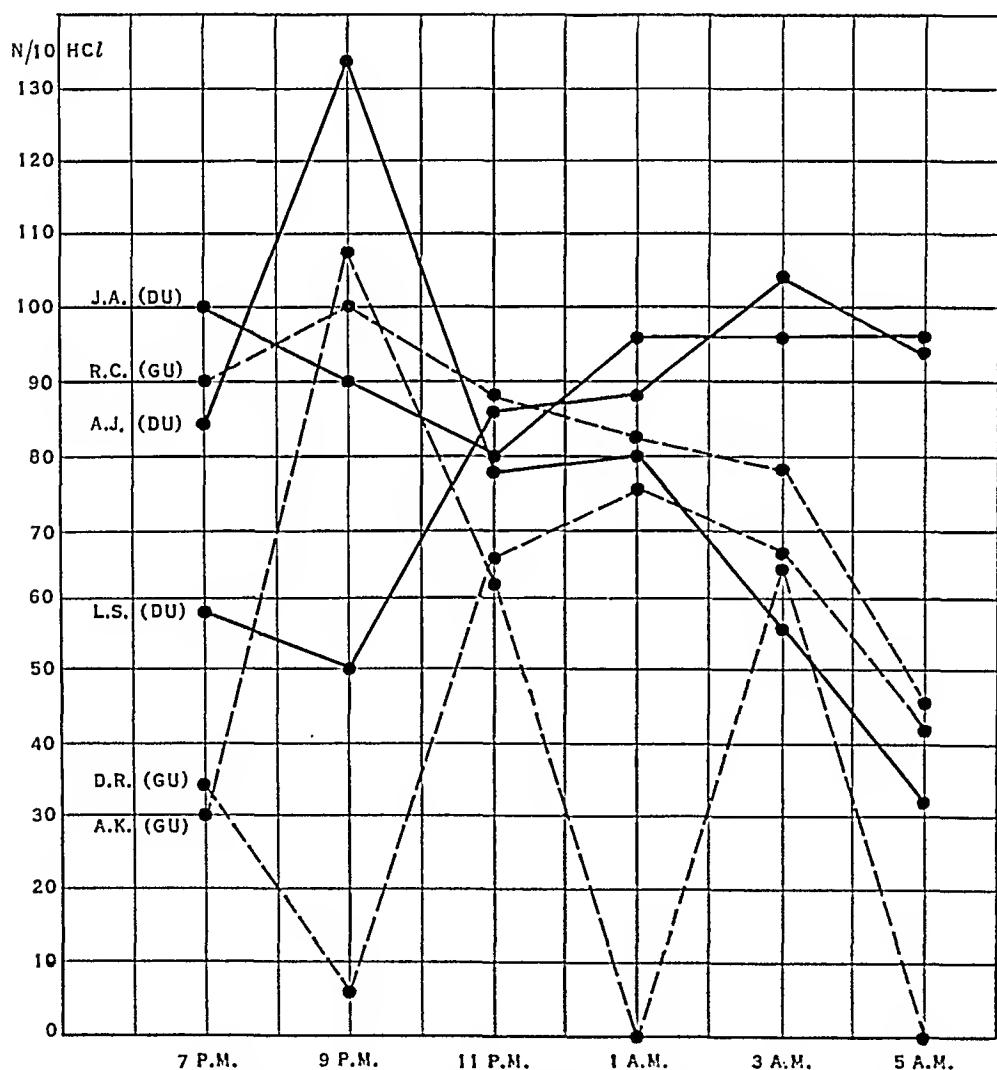


CHART III.—Very high curves of free hydrochloric acid in ulcer patients during the night. Test as described in Chart II.

of 30 drops a minute (Chart VI). Thus the patient receives 3 quarts of milk and 15 gm. of bicarbonate of soda per day. Such a solution will theoretically neutralize 9 quarts of $\frac{N}{10}$ hydrochloric acid. Actually, many interval samples revealed an absence of free hydrochloric acid with a low total acidity. Certain obvious difficulties

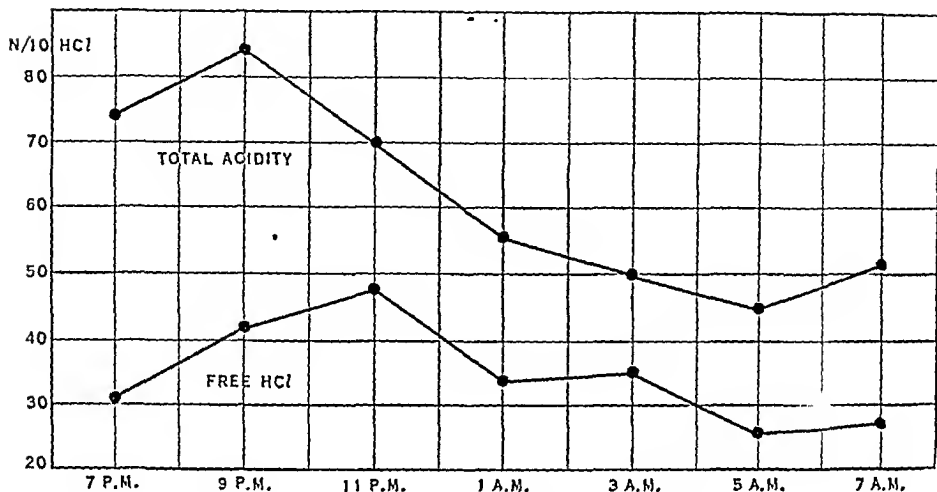


CHART IV.—Night Refruss test—composite curve in 14 gastric ulcer patients. Test as described in Chart II.

in the treatment will be avoided if the following procedures are added: (1) Accustom the patient to the tube by doing a day and night fractional test meal first. (2) After 48 hours of the drip, study the chemistry of the blood, particularly its alkalinity. (Carbon dioxid combining power.) If this approaches 80 volumes per cent or if symptoms of alkalosis appear, decrease the alkali. In our series there were no symptoms. The carbon dioxid combining

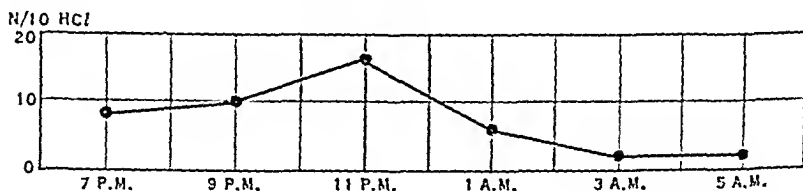


CHART V.—Night Refruss test—composite curve of free hydrochloric acid in 10 miscellaneous controls. Test as described in Chart II.

power varied from 60 to 70. The urine, of course, became alkaline while the blood urea and chlorids remained normal. (3) Use sedatives. (Luminal during the day and a hypnotic at night.) (4) For dryness of the throat, an occasional sip of the mixture is permissible (but not desirable).

As obvious adjuvants to the treatment, local heat is applied to the abdomen and atropin, gr. $\frac{1}{8}$ to $\frac{1}{160}$, t. i. d. or q. i. d. (by hypodermic or mouth), is administered. The chill should be removed from the milk and the drip given continuously throughout the day and night. To prevent psychic secretion, and this is a point of considerable importance, food should not be seen nor discussed.

As a rule, the patients tolerate the tube nicely. That this would occur we knew from experience with the Einhorn treatment. There the tube is allowed to remain in the duodenum 3 weeks. Einhorn

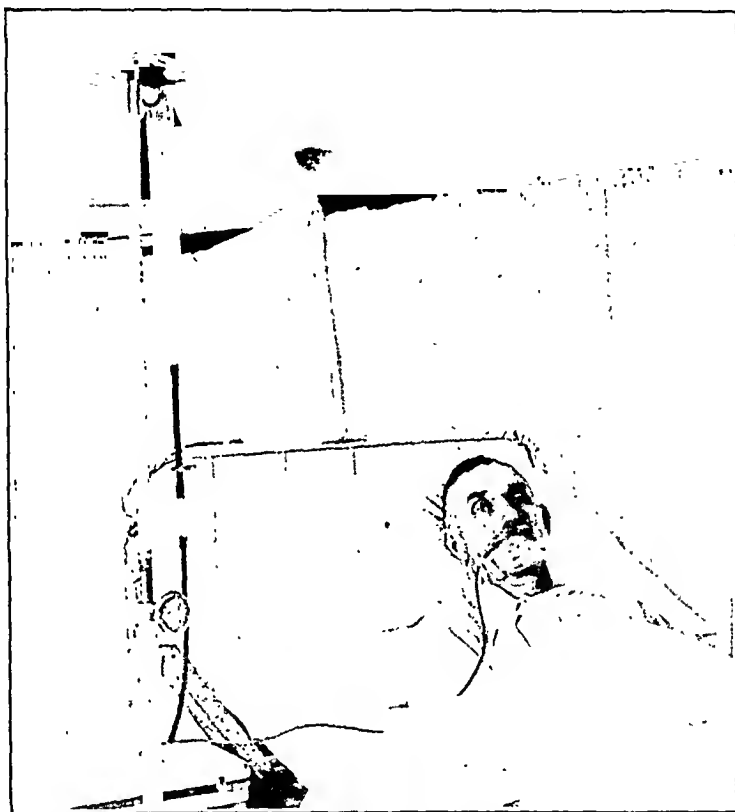


CHART VI.—Patient with duodenal ulcer undergoing the treatment. Note that he appears perfectly comfortable.

and his followers have treated an enormous number of patients in this fashion without any difficulty. The author, personally, has had no difficulty in continuing the treatment uninterruptedly for a period of 2 to 3 weeks. Then the tube is removed during the day. The patient receives conventional ulcer therapy consisting in bland feedings every hour or every 2 hours (with alkalis and atropin) from 8 A.M. to 8 P.M. At 8 P.M. the drip is again started. At the end of 4 weeks a second night fractional test meal is obtained and a radiologic checkup. The treatment is continued then according

to the indications. Several patients, on discharge, have continued for several months to take the milk drip on retiring.

Results. During the past 22 months we have treated 42 patients—18 duodenal ulcers, 19 gastric ulcers and 5 jejunal ulcers. The entire group consisted of adult males whose age averaged 43 years. In the duodenal ulcer group the average duration of symptoms was 4 years and 3 months. Ten patients are symptom-free for 3 to 6 months, 3 patients for 1 year, 3 for 1½ years, 1 for 2 years and 1 for 3 years. In 3 instances the radiographic signs, that is, an

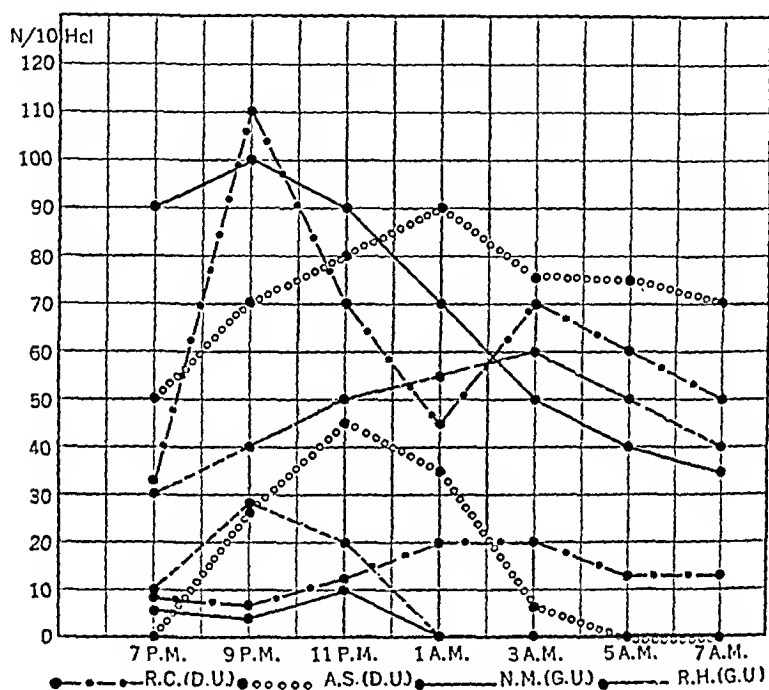


CHART VII.—The upper curves show the high point of free hydrochloric acid in the night Reflux before the drip treatment. The lower curves show the night Reflux curves of free hydrochloric acid after 3 weeks' drip treatment. Tests as described in Chart II.

irregular duodenal bulb, disappeared at the end of 3 weeks of the treatment. In 16 patients with gastric ulcer the duration of symptoms averaged 6 years. The follow-up reveals that 4 are well at the end of 3 months, 5 at 6 months, 5 at 9 months, 1 at 18 months and 1 at 22 months. Radiographically, the ulcer niche diminished considerably in size in 5 cases and disappeared completely in 11 cases. One patient (C. D.) with a large gastric ulcer near the cardia lost his symptoms and the niche for 4 months. Then his wife's death, a separation from his children and the loss of his job,

were followed by a recurrence of the lesion. Again his symptoms and signs disappeared with the drip treatment. Four patients with large jejunal ulcers after partial gastrectomy were treated. Radiographically, the ulcer pockets disappeared completely and, clinically, 1 is well at 9 months, 1 at 6 and 2 at 4. Several other patients have been treated recently, but since the follow-up is less than 3 months the observations on them will not be cited now.

Among the features of these cases worthy of comment are the following: (1) The loss of all symptoms in 4 to 6 hours after the institution of the drip is striking. (2) The complete comfort (including excellent sleep) of almost all the patients while on the drip. (3) The eagerness to return to the drip on the recurrence of even slight symptoms. (4) In several instances where no relief was obtained from the Sippy or mucin treatment, immediate improvement followed the drip treatment. (5) In many instances disappearance of the radiographic signs of the ulcer. (6) Although the subsequent course is not long enough to justify a conclusion, with one exception, no definite recurrences have been noted. (7) The willingness on the part of several of the patients to continue the drip at home at night (thus continuing an ideal ulcer therapy for long periods while pursuing their ordinary daily occupations).

Of course, one should point out the following to temper the above: (1) The method is somewhat inconvenient to the patient. (2) It is not an ambulatory method. (3) One must consider the striking tendency of ulcer to recur after any form of medical therapy. (4) The probable intolerance of some patients to milk. (5) A larger series of cases and a longer follow-up study is necessary before drawing definite conclusions.

It is hoped that the following will be realized: (1) That this is a logical and practical method of producing constant achlorhydria. (2) That the habit of secreting less acid (by lessening psychic secretion during the day and fasting secretion during the night) will be instituted in the patient (Chart VI). (3) That it affords a simple method of ideal self-treatment of the ulcer patient without stopping his daily activities.

Summary. 1. The rôle of the acid factor in the pathogenesis and therapy of peptic ulcer is discussed and its importance stressed.

2. Some basic studies in gastric secretion are presented, illustrating the rôle of the nervous system (vagus nerve) and the acidity curves during the night.

3. Because of these facts, a new method of ulcer therapy consisting in a continuous drip, 24 hours daily, of alkalinized milk into the stomach is advocated on the basis of the results obtained in 42 cases treated in this way.

THE PREDIABETIC STATE: ITS RELATION TO OBESITY AND TO DIABETIC HEREDITY.

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IMPAIRMENT of carbohydrate metabolism exists in various degrees, the more marked of which are grouped in the disease entity, diabetes mellitus. There are no particular standards of blood or urine sugar determination which set this stage of impairment apart, since there is no perfect definition of diabetes mellitus. The same state of affairs exists in the milder portion of the impairment scale. Hence, the classification of the individual case as normal, prediabetic or frank diabetic depends largely upon the judgment of the clinician.

Regardless of classification standards, no one denies that, satisfactory as the treatment of diabetes mellitus is, the result of dietary therapy for the incipient impairment of the prediabetic group is excellent. Slight restrictions in the dietary, either specifically or generally, usually suffice. It is not to be supposed that all prediabetics are expected to proceed along the impairment scale eventually to become frank diabetics, but a number do, and these cannot be predicted in advance, so that treatment must be instituted for all. The restrictions involved, far from doing harm, can be said to be worth while in either case.

The prediabetic state is easily detected by any carbohydrate tolerance test. The usual examinations of the fasting blood and of the urine specimens for sugar content are of little use in this condition. The earliest evidences of carbohydrate metabolism impairment may be expected to be found in the postprandial blood sugar determination at approximately 2 hours following any meal of the day, but for purposes of standardization and statistics some variety of a tolerance test is desirable. No symptoms referable to the impairment are present at this stage of the disease. Selection of cases for the test must be made, therefore, from those groups which are known to present an increased incidence of prediabetes. These have often been described. Obesity and diabetic heredity are usually thought to be high in incidence of prediabetes. The present study has been undertaken to determine the extent of these factors in a controlled series of 500 cases each of normal and prediabetic carbohydrate tolerance curves.

Method. The Brill test meal¹ is used as a test of the carbohydrate tolerance in this clinic. The method and the interpretation

of the results have been studied by Hubbard and Wright,² who believe it to be quite as satisfactory as any carbohydrate tolerance test.

The subject fasts from the evening before until the morning of the test when a urine sample is collected, blood is taken from the basilic vein for blood sugar estimation and the breakfast test meal of 100 gm. of carbohydrate, 25 gm. of protein and 25 gm. of fat, totaling 725 calories, is eaten. Two hours later the second or postprandial blood specimen is taken, and the urine is saved for 4 hours following the breakfast. Most knowledge of the state of carbohydrate metabolism is learned from the blood sugar estimation, especially the postprandial. Qualitative test for glucose in the urine is done, but little valuable information is thus obtained.

The Benedict copper method is used in the estimation of the blood sugar content,³ the fasting normal of which is 70 to 90 mg. per 100 cc. of blood. The normal postprandial or second blood sugar estimation for the test by this method has been said to be not over 100 mg.² No matter what the fasting determination may be, the test is said to be normal if the second estimation is normal and the latter really determines the normality or abnormality of the test.

That group is considered prediabetic which has readings of over 100 mg. and under 150 mg. for the second blood sugar. The fasting blood sugars for this group are largely normal; some are raised slightly. About 25 per cent of these prediabetics have sugar in the urine after the test. We do not believe that anyone would label this section as frank diabetic, but some may consider the normal line too finely drawn with many cases on the borderline between normality and the abnormality of prediabetes. However, one must have definite standards for statistical study and an attempt has been made to select as prediabetic a group above the set normal and below the genuinely diabetic.

Five hundred cases classified by the above standards were studied from each of the normal and prediabetic curve groups. The entire 1000 cases are part of a large series of patients who were thought to have possibly a prediabetic curve and in whom carbohydrate tolerance tests were made, but aside from this the cases are unselected. The case record of each was studied and examined for age, sex, height in feet and inches without shoes, weight without clothing, diabetic heredity and diagnosis. Actual weight was compared with normal weight;⁴ the difference was evaluated in per cent above or below normal weight. Normal weight is considered in this paper to be within 5 per cent above or below exact normal weight, obesity 6 per cent or more above exact normal and underweight as 6 per cent or more below exact normal. "Thin" is sometimes used to include both the normal and underweight groups.

The heredity discussed in this paper is taken to be direct heredity from parents; any other heredity is termed familial and includes the history of the disease in brothers, sisters, aunts, uncles and cousins.

Tabulations were made of the weight and heredity factors in the normal and in the abnormal or prediabetic curve groups. Various correlations were attempted and the most significant are discussed below.

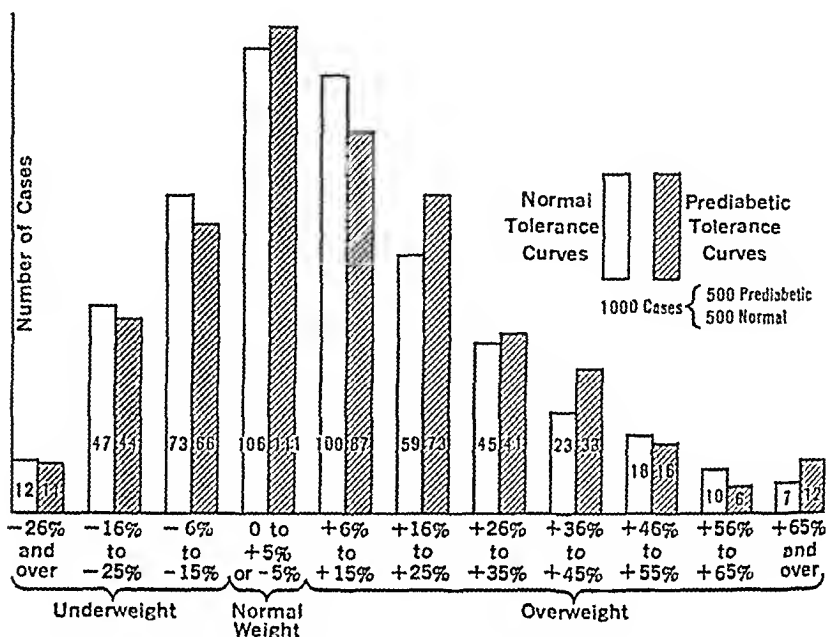


CHART I.—Comparison of normal and abnormal cases in various weight groups.

Data and Interpretation. Prediabetes is found in 47 per cent of all the cases selected for the tolerance test in this clinic. We again emphasize the selection of cases and believe that the figure given is variable and depends upon it.

	Normal Curves			Prediabetic Curves		
Both Sexes	52	22	26	54	22	24
Males	49	20	31	51	25	24
Females	55	22	23	55	21	24

Per cent Overweight Normal Weight Underweight

Males - 194, Females - 306, in both Normal and Prediabetic Groups.

CHART II.—A condensation of Chart I with further division into sex.

A comparison is made in Chart I between the number of normal and abnormal cases in various weight groups of the main weight

divisions. There is seen to be no constant relation between body weight and type of tolerance curve, except a minor correlation in the underweight.

Chart II is actually a condensation of Chart I, with further division into sex. Within minor nonclinical variations there are no more obese cases in the abnormal (prediabetic) than in the normal group, no more normal weight cases are in the abnormal than in the normal group and there are no more thin cases in the normal than in the abnormal curve group. Sex makes no difference except in the male underweight group, and then the difference is not striking. The average gross distribution in the abnormal and normal curve groups shows about 50 per cent of each are obese, 25 per cent normal in weight and 25 per cent underweight. When

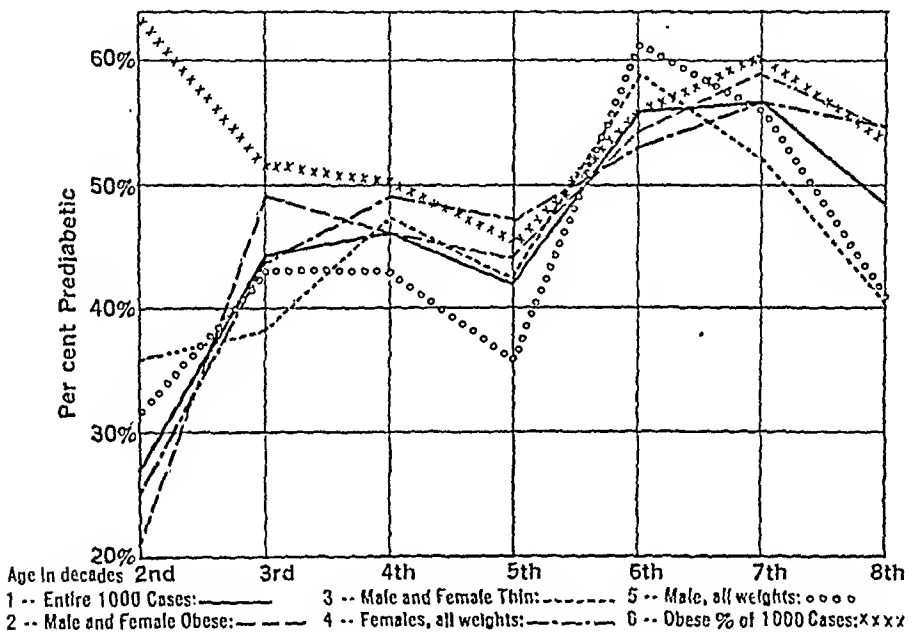


CHART III.—Analysis of abnormal curve cases by decades.

considered alone the prediabetic section is obese; comparatively, however, there is no difference between it and the normal curve group.

A series of curves are plotted in Chart III to show the percentage of abnormal curve cases by decades in: (1) The entire 1000 cases; (2) all the obese; (3) all the thin (normal or subnormal weight); (4) females of all weights; (5) males of all weights. Another (Curve 6) points out the percentage of the 1000 cases which are obese at each decade. The main course of each of Curves 1 through 5 is the same; the variations from it are not great and in general the correlation of abnormality of curve seems to be with age, with the peak in the 7th decade and a later fall. The high percentage of obese subjects in the 2d decade is obviously untrue and due to

selection of obese for the test. There appears to be a slight tendency in the 7th and 8th decades for prediabetes to be associated with the higher rather than the lower weights, and also with the female sex. The number of cases involved in this portion of the graph is necessarily not great, the trend itself is not marked and of no clinical although perhaps of academic importance. Grossly, then, the variable incidence of prediabetes is associated with age and not with body weight or sex.

To prove or disprove the hypothesis that the greater the weight, the higher might be the second blood sugar reading within our prescribed limits and contrariwise for underweight, a graph (Chart IV), which compares the weights of the prediabetic curve group with blood

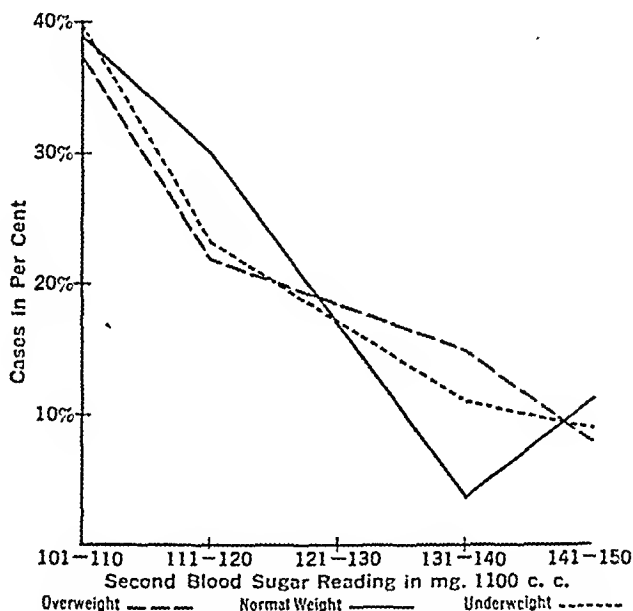


CHART IV.—Comparison of weights of the prediabetic curve group with blood sugar readings.

with blood sugar readings, was made. The majority are found below 120 mg. Only 250 cases are considered in this chart and hence the plottings for 140 to 150 mg. are slightly inaccurate (due to the small number of cases) except for the obese group which contains about twice the number of cases found in the other 2 groups as we have seen in Chart II. There is no distinct correlation between these factors as considered above.

All data on heredity are included in Chart V. Part *A* demonstrates the larger percentage of abnormal curves in the direct hereditary group and in the combined direct and familial hereditary group but not in the familial group. Part *B* determines that the prediabetic state is more common in the obese than in the thin

(normal or underweight) and that the direct hereditary group as a whole is 66 per cent obese compared with 53 per cent in the entire prediabetic group. The number of abnormal curves for each decade is compared with the number of normal curves in the obese in Part *C*, in the thin in Part *D* and for all weights in Part *E*. Obviously the obese show a higher incidence of prediabetes when direct heredity is present.

Discussion. Briefly, obesity is not intimately associated with the prediabetic state nor underweight comparatively unassociated with it. The incidence of prediabetes for each weight group is the same within clinical limits. The thin subject is just as apt to be prediabetic as the fat subject at the same age.

CHART V.—DATA ON HEREDITY.

A				B			
Type heredity.	Total cases.	Normal.	Prediabetic.	Type curve.	Direct heredity.	Obese.	Thin.
Direct heredity	73	45%	55%	Prediabetic		73%	27%
Familial heredity	32	53%	47%	Normal curve		58%	42%
Combined fam. & dir.	12	42%	58%	Both pre and norm.		66%	34%

Direct heredity.										
	Decade.	2d	3d	4th	5th	6th	7th	8th	Total cases.	Per cent.
C—Obese	Normal	0	2	4	3	8	2	0	19	40
	Prediabetic	0	0	7	6	13	3	0	29	60
D—Thin	Normal	1	2	2	4	4	1	0	14	56
	Prediabetic	2	3	2	0	2	1	1	11	44
E—All weights	Normal	1	4	6	7	12	3	0	33	45
	Prediabetic	2	3	9	6	15	4	1	40	55

Prediabetes shows an age correlation for all sexes and all weights except for minor variations in the 7th and 8th decades, as shown above.

Cases of heredity of the direct type present an increased incidence of prediabetes; the familial type does not. In the direct heredity group obesity shows a higher incidence and underweight a lower incidence of the disease. Strangely enough, the direct heredity group is more obese than the whole group of 1000 cases; the latter presents about 53 per cent obesity and the former about 66 per cent obesity. This may be a matter of training in eating habit, selection of cases or of metabolism. The importance of diabetic heredity is becoming more evident as time goes on.⁵ More and more is diabetes being found to have an hereditary background, although not distributed according to the Mendelian law.⁶

When considered practically, the data on prediabetes, age and body weight suggest that body weight cannot be used as a criterion for selection of cases for the carbohydrate tolerance test in the detection of prediabetes but that, regardless of body weight, a larger percentage of prediabetics may be expected in the older age groups.

tender. The heart apex was in the fifth interspace in the midclavicular line. The heart sounds were of good quality with the first sound booming at the apex. There was a soft, nontransmitted bruit at the apex. The abdomen was tense and slightly distended, and markedly tender. The veins over the abdomen and lower chest were moderately dilated. The liver and spleen were not palpable. The right ear drum was normal but the left was dull. There was a left mastoid scar.

Past History. The patient had always been well except for an attack of measles complicated with a left otitis media and mastoiditis necessitating a mastoidectomy.

Admission Diagnosis. Toxic scarlet fever with acidosis; general peritonitis; questionable streptococcemia.

Temperature, 101.2° F.; pulse, 88; respirations, 24. The white blood cell count was 24,600 with 87 per cent neutrophils. Urine showed a trace of albumin with 20 white cells and 4 red cells per high power field. Throat culture showed hemolytic streptococcus predominating. Blood culture was sterile 1 week later.

Following negative conjunctival and intracutaneous sensitivity tests to horse serum, patient was given 10,000 units of scarlet fever antitoxin intramuscularly and 2500 units intravenously. Thirty-five minutes after the antitoxin was administered the patient had a severe reaction manifested by a chill, marked cyanosis and thready pulse, lasting about 15 minutes. Due to the serious condition of the patient, the laparotomy was postponed. The next day, the sixth day of her illness, the patient showed early signs of bronchopneumonia in the right lower lobe. A Roentgen ray taken of the abdomen showed a marked dilatation of the stomach with fluid in the abdominal cavity. The white blood cell count was 28,600 with 85 per cent neutrophils.

Laparotomy. Right rectus incision was made; the rectus was retracted. On opening the peritoneum, a thick seropurulent fluid gushed forth under marked pressure. Thick grayish-white fibrinopurulent exudate covered the exposed visceral peritoneum. The parietal peritoneum was covered with a thinner layer of exudate. The intestines not covered with exudate displayed a bright red, fiery appearance. The appendix was normal, except for some redness of the serous covering. The fluid was odorless. The appendix was removed. Three cigarette drains were inserted. The fibrinopurulent exudate resembled a pseudomembrane of varying dimensions, in some places being $\frac{1}{4}$ inch in thickness. The section of the fibrinopurulent exudate was composed of neutrophils for the most part. The section of the appendix was normal, except for the serosa, which showed an inflammatory process. The culture of the fluid was a hemolytic streptococcus.

On the 7th day temperature rose to 105.6° F. The rash had markedly faded. The patient vomited twice. Transfusion of 330 cc. of whole blood was given as well as 900 cc. of hypodermoclysis of 5 per cent glucose in saline. Blood culture was also taken, and was sterile 1 week later. On the 8th day the patient had a bilious emesis, and was given a gastric lavage; 9th day, had marked diarrhea having 8 stools; 10th to 13th day, had 10 to 13 stools daily. Urine was free from albumin. Temperature ranged between 105.6° and 101.8° F. Patient was better; 17th day, diarrhea ceased; 33d day, blood culture was taken, which was sterile 1 week later; 17th to 47th day, had a temperature between 103° and 99.4° F. and was gradually improving; 47th day, was discharged against advice. The wound had completely healed 2 months after her dismissal from the hospital. The patient has been well ever since.

CASE 2.—A baby boy, aged 20 months, was admitted to the hospital on January 12, 1931 (13th day of illness) with a history of cold, cough, fever

TABLE 1.—PERTINENT DATA OF CASES REPORTED IN LITERATURE.

Author.	Age.	Sex.	Onset.	Treatment.	Appendix.	Results.	Findings.
Moore ^{2a}	Not stated	F.	12th day	Not diagnosed during life	No mention	Died 16th day	Large abdominal effusion; spleen very large and mushy; covered with great amount of fibrinous exudate; peritoneum in places covered with plastic exudate.
Breton ²	19	F.	19th day	Medical	Recovered, 26th day	
Breton	21	F.	5th day	No mention	Died 8th day, 24 hrs. after admission	Marked congestion of peritoneum covered with fine, fibrinous exudate; fluid almost transparent; intestines congested.
McCollom and Blake ¹³	5	M.	28th day	48th day, paracentesis, 21 oz. of pus; 49th day, rupture of umbilicus	No mention	Recovered	Streptococcus pyogenes in fluid.
McCollom and Blake ¹³	31	M.	24th day	Laparotomy	Normal	Died	Thin pus, followed by cord-like substance; intestines red, congested; fibrin layer on diaphragm, spleen, liver.
Hecker ⁹	2½	M.	Eruptive stage	Medical	No mention	Died	No mention.
Ghon, cited by Hecker	7½	M.	Eruptive stage	Medical	No mention	Died	No mention.
Teissier ²⁵	7 m.	Not stated	Not stated	Medical	No mention	Died	No mention, but speaks of streptococcus being the secondary invader.
Teissier	6	Not stated	Not stated	Medical	No mention	Died	All Teissier's cases except one were discovered postmortem.
Teissier	15	Not stated	Desq. period	Medical	No mention	Died	
Teissier	28	F.	12th day	Medical	No mention	Died	
Teissier	12	F.	15th day	Medical	No mention	Died	
Tournine and Fenestre ²⁷	14	M.	2d day	See findings	Appendiceal abscess	Recovery 4th day, much better	Operated on 14th day previously for an appendiceal abscess and was still draining at onset of scarlet fever.
Dunham ⁴	5	F.	14th day	Laparotomy	Slight fibrinous peritonitis otherwise norm.	Recovered	Free pus in right pelvic fossa, odorless; right tube markedly injected, deep red, adherent to surrounding structures by delicate fibrinous adhesions, denser here than throughout the rest of the peritoneal tract; culture of the fluid was a hemolytic streptococcus.
Platon ¹⁷	3	F.	29th day	Medical	Surface congested, covered with fibro-purulent exudate	Died 40th day	Intestines covered with extensive fibrino-purulent exudate; subphrenic and pelvic abscesses; patient had vaginitis from the 10th day, the smear of which showed Gram-positive cocci.
Fjelde ⁶	3	F.	12th day	Laparotomy 49th day	No mention	Recovered	Abscesses right lower quadrant and right upper quadrant; intestines matted together; gastric retention, 47th day; culture of the fluid was a green-producing streptococcus with a foul odor.

Out of 5500 cases of scarlet fever occurring at the Willard Parker Hospital from 1928 to 1932, we have seen only 3 cases of primary peritonitis. However, there were many other cases of secondary peritonitis due either to the suppuration of mesenteric or retroperitoneal lymph nodes, or to appendicitis, or to an extension from a local process as from an abscess or from an osteomyelitis of the hip.

and rash. *Past history:* Patient has always been well except for an attack of measles at 13 months. *Physical examination on admission:* Patient was a marasmic, rachitic, acutely ill, pale, baby boy with typical pneumonic facies. There was a fine desquamation on the body. The tongue was of the strawberry type. The tonsils were mildly congested and considerably enlarged but not adherent to pillars. There was a punctate enanthem on the soft and hard palate. Tonsillary glands were small-pea size and slightly tender. The heart apex was in the 5th interspace just outside the mid-clavicular line. The first heart sound at the apex was booming. There were signs of bronchopneumonia in the left lower lobe. Liver was at the costal margin. Spleen could not be felt.

Admission Diagnosis. Scarlet fever with bronchopneumonia in the left lower lobe.

Urine showed a faint trace of albumin. Throat culture showed a hemolytic streptococcus predominating. On the 16th day he ran a double remittent type of fever; 104° to 100° F.; 104.4° to 101° F.; 17th day, had marked anorexia; 18th day, vomited and showed signs of bronchopneumonia in right lower lobe. Blood culture was positive for hemolytic streptococcus; 19th day, vomited; 21st day, vomited again. He was given a transfusion of 120 cc. of whole blood. Temperature ranged between 105° to 98° F. from 15th to 22d day; 23d day, had 3 loose greenish stools. Up to this time patient had 2 to 3 stools daily, but they were all well formed and of a yellowish color. White blood cell count was 23,450, with 78 per cent neutrophils, 18 per cent lymphocytes, and 6 per cent mononuclears. Red blood cell count was 4,240,000 with hemoglobin 50 per cent; 24th day, thoracentesis of left chest was done and 20 cc. of thick, greenish-yellow fluid with a brownish tinge was removed, the culture of which was hemolytic streptococcus. White blood cell count was 10,250, with 61 per cent neutrophils, 33 per cent lymphocytes, and 6 per cent mononuclears. Red blood cell count was 3,270,000 with 55 per cent hemoglobin; 25th day, thoracentesis of left chest was repeated and 170 cc. of a thicker but similar fluid was withdrawn. Transfusion of 120 cc. of whole blood was given. Anorexia was less marked; 26th day, was more alert. Urine showed a trace of albumin with 3 white blood cells and an occasional red cell per high-power field. The red blood cell count was 4,930,000, with hemoglobin 70 per cent; 27th day, patient died. Eleven hours prior to death, patient vomited a watery material with few milk curds; 9½ hours later he vomited again, but this time a dark, brownish fluid. Abdomen was not remarkable 6 hours before death. Temperature, 103° to 99.8° F. (23d to 27th day.)

Necropsy. On opening the peritoneal cavity, about 400 cc. of yellow, slightly turbid, fluid was found. There were profuse, fine, soft, fibrinous adhesions matting together the intestines and involving all the abdominal viscera except the kidneys. The visceral peritoneum and mesenteric lymph nodes showed an acute congestion. The nodes were large and soft. The appendix was normal although retrocecal and attached by soft adhesions. No primary focus for the peritonitis could be found.

Histologic sections of the peritoneum showed an acute inflammatory process. There was a thick or thin layer of fibrin on the surface. This frayed out on the free surface, where it was laid down in the characteristic shingled fashion and showed extensive hyalinization. In the meshes of this fibrinous exudate were many leukocytes, but toward the peritoneal surface there was a considerable infiltration of mononuclear inflammatory cells as well. The serosa itself in many places was destroyed and the peritoneal cells missing. There was considerable edema with delicate fibrin network in the areolar subperitoneal tissue.

Another interesting and unusual thing which transpired at the autopsy was the finding of an erosion of the esophagus about the size of a quarter-dollar posterior to the left ventricle.

CASE 3.—A young adult woman, aged 32 years, was admitted to the hospital December 20, 1931, from one of the city hospitals, with a diagnosis of scarlet fever and ectopic pregnancy, and with the following history: On December 12 the patient had a sore throat and malaise; December 13 the sore throat was worse and a rash appeared on her body; on the 14th she had bleeding from the vagina; on the 19th she had severe pain in the abdomen and vomited thrice. The vaginal bleeding persisted daily, but began to decrease, and on the 19th was very slight. She had had 3 children: the first, 9 years ago, and the last, 2 years ago. Menses have always been regular, last time November 27, 1931. Patient has always been well.

Physical examination on admission showed a well nourished and developed young adult woman, acutely ill, alert, and complaining of pain in her abdomen. The skin was covered with a fading, scarlatinal, hemorrhagic eruption. She was beginning to desquamate on her neck. There were also a few urticarial wheals over the body. The tongue was of the strawberry type. There was a moderate congestion of fauces and pharynx with a punctate enanthem on soft and hard palate. The tonsils were slightly enlarged and congested but neither cryptic nor adherent to pillars. The tonsillary glands were large-pea size and tender. The abdomen was slightly tense, being tender all over, but chiefly in both lower quadrants, especially the right. Rectal examination was negative except for tenderness which was more marked in the right lower quadrant. Chest and neurologic examinations were negative. There was no bleeding from the vagina, but there was a small amount of blood in the vagina. Temperature, 104° F.; pulse, 132; respirations, 28; white blood cell count was 26,000 with 95 per cent neutrophils; urine was negative.

Admission Diagnosis. Scarlet fever with an acute abdomen and urticaria. Throat culture showed a hemolytic streptococcus predominating. Blood culture was sterile 1 week later.

Laparotomy. A lower midabdominal incision was made. The peritoneum was opened and about 500 cc. of free seropurulent, greenish-yellow, odorless fluid was found in the peritoneal cavity. The visceral and parietal peritoneum was red and congested, but no fibrinous exudate was found. Appendix was normal. The appendix was removed. The stomach, tubes, ovaries and gall bladder were normal. Two large cigarette drains were inserted. Culture of the fluid gave a hemolytic streptococcus. Patient was immediately given a hypodermoclysis of 2000 cc. of 5 per cent glucose in saline. The next day the patient was worse with the temperature rising to 105° F. White blood cell count dropped to 5900 with 95 per cent neutrophils red cell count was 3,990,000 with 65 per cent hemoglobin. Blood culture taken again was sterile a week later. Following negative conjunctival and intracutaneous tests to horse serum, patient was given 20,000 units of scarlet fever antitoxin intramuscularly. She was also given a hypodermoclysis of 1000 cc. of 5 per cent glucose in saline, followed by an infusion of 500 cc. of 10 per cent glucose in saline. Immediately following the administration of the infusion, the patient had a mild rigor, lasting about 15 minutes, and appeared much worse. She died 2½ hours later, having a temperature of 109° F. Necropsy could not be obtained.

Discussion. Except for a small contribution which bacteriology has made, there has not been anything really added to further the knowledge of this condition since Breton wrote his essay in 1888. The signs and symptoms as well as the etiology, pathology and treatment were fully described by him. Diarrhea, which had occurred in both of his patients, was the symptom he had stressed the most. The authors of the other cases, with two exceptions, did

not even mention this symptom. On the other hand, we noticed it in 2 of our 3 cases.

An interesting question suggests itself in the endeavor to solve the mode of transmission of the etiologic factor. How does the peritonitis arise if there is no local abdominal focus to be found? The various pathways to be considered are the blood stream, lymphatics, or direct extension either from the mouth or from the genital channels. Flexner,⁷ who considered a primary peritonitis to be an infection arising either from the blood stream or the lymphatics, stated that it occurred only as a terminal event, following a prolonged illness. This correlation apparently does not seem to fit any of these reported cases, except one of ours, as they evidently had all been in good health prior to the onset of the scarlet fever. This appears to be substantiated by authors (Grawitz,⁸ Herrenschmidt,¹⁰ Rabinowitz,¹⁸ and Schwartz²¹) in their writings on primary streptococic peritonitis, a condition, though highly similar, yet occurring ever so much more frequently. They favor the hematologic route as being the transmitter of the etiologic factor. Kunzel,¹¹ through his gross pathologic, microscopic and bacteriologic studies, believes that he has disproved the gastric and intestinal origin, for he failed to find any intermediary abdominal focus, as his cultures of the appendix, uterus, spleen, intestines, tubes and ovaries were sterile, whereas those of the peritoneal exudate and nasopharynx showed streptococcus. He claims that this is absolute evidence of blood stream infection. On the other hand, although we are inclined to consider this route the most likely, it does not appear to be the exclusive one, for out of a series of 5500 cases of scarlet fever there were 42 cases which had a hemolytic streptococcemia during life, but only 1 of these showed a general peritonitis at autopsy. Such an infrequency would tend to indicate a none too low, if not a high, resistance-coefficient on the part of the peritoneum against any pre-agonal or agonal infection from the blood stream. Moreover, the several blood cultures taken from our other 2 cases were all sterile. This would tend to discredit the hematogenous route, although it would not disprove it, for not infrequently, even if the blood stream is not sterile, one is not able to obtain from blood taken out of a peripheral vein a sufficient number of organisms to yield a positive culture.¹⁶ The other writers apparently did not take any blood cultures as not a single writer even mentioned them. If the lymphatics are the conveyors, they can be palpated either by rectal examination or during a laparotomy, or both, and also on the postmortem table, procedures each of which we had the opportunity to verify on 2 cases which will be published later.

Favoring a direct extension appears to be the work of McCartney,¹² who recovered from peritonitis in monkeys the same strain of pneumococcus that he had introduced into the vagina 3 days previously, and by both bacteriologic and pathologic studies showed that the

organism passed by way of the uterus and tubes without causing any appreciable local inflammation. From this investigation he concluded that primary pneumococcus peritonitis in the female arises from the genital route. To a certain degree his work might be given some credence statistically by the slight increase of the incidence of this condition in the female (Ehringer,⁵ Rischbieth¹⁹). The latter reported that out of 57 cases of primary pneumococcus peritonitis which he had collected, the incidence was slightly higher in the female under 10 years of age. Because all of his streptococcus peritonitides had occurred in the female, Armstrong¹ insisted that the Fallopian tubes were the path of the invader. But his series was limited to only a few cases. Nothnagel¹⁵ stated that the streptococcus was swallowed with the sputum and by wandering out through the stomach wall reached the peritoneum. Touraine and Fenestre considered it due to presence of the eruption on the peritoneum or in the lymphatics and they claim that it ought to be differentiated from secondary peritonitis occurring during the desquamating period, which is grave. It might be added here that there might be a question whether Touraine and Fenestre's case was a true case of general peritonitis, as the patient recovered so rapidly, being almost symptom-free the fourth day.

Out of the total of 19 cases of primary peritonitis associated with scarlet fever only 1 was reported as having a vaginitis, the smear from which showed Gram-positive cocci. Furthermore, the difference of incidence in the sexes is not remarkable. So what part direct extension may play in this condition remains unsolved, although it must remain as a consideration. Is it possible that in these few cases the peritoneum had lost its resistance to infection, or is it originally weak, having a congenital or acquired predisposition to hemolytic streptococci? Or is it a certain type of organism having a specific affinity for the peritoneum which cannot as yet be differentiated by the present bacteriologic and immunologic means?

From the pathologic viewpoint, there is at first a generalized vascular congestion which is more marked on the visceral peritoneum and greater omentum (Breton) than on the parietal, with little or no deposition of fibrin. The fibrinous exudate forms adhesions between the intestines which soon (24 to 48 hours) accumulate rapidly to form a thick fibrinopurulent exudate simulating a pseudomembrane of varying dimensions, at times as much as $\frac{1}{4}$ inch in thickness. Simultaneously, an excess amount of fluid is formed, thin and serous at first, then seropurulent yellowish to green tinged, and finally purulent. The fluid is not very abundant, although occasionally, as in the first case cited, a large effusion may be present, the fluid gushing forth under marked pressure as soon as the abdominal cavity is opened. Histologic sections of the thick, fibrinopurulent exudate show a great preponderance of neutrophils

while those of the peritoneum show an acute inflammatory process, fully described under Case 3. Similar if not identical findings have been reported by the writers on primary streptococcic peritonitis, as Herrenschmidt and others previously mentioned. The appendix is grossly normal except for similar exudate on the serosa, or if no exudate is present there is only a vascular congestion of the serosa. Cultures in the various cases from the literature are not accurate except in 3 of the cases. However, the others all state that the streptococcus is the secondary invader; although whether they had attempted to culture or examine the organisms, the majority of the writers do not state.

Referring to treatment, Breton first recommended paracentesis when the fluid was purulent, and repeated when necessary and, if the fluid persisted, laparotomy. However, how he came to this mode of treatment (he did not use it on either of his patients) he did not relate, nor did he state whether it had ever been used by anyone else. A few, as Ruppaner,²⁰ claim that there is no reason to operate as there is no abdominal focus. But how the body could take care of such thick plaques of fibrinopurulent exudate as we found in one of the cases, appears to be a question. Besides, there is a peril, and a rather constant one, that one or more of these adhesions might cause an intestinal obstruction, as reported by Fjelde. However, the results of the treatment are the most convincing, for of the 6 patients who recovered, all had external drainage of the peritoneal cavity except one. "Ubi pus, ibi evacuatio."

Conclusions. A review of the literature shows that primary peritonitis complicating scarlet fever is a rare occurrence of grave prognostic import.

Three cases of this nature which had developed in a series of 5500 cases of scarlet fever occurring at the Willard Parker Hospital from 1928 to 1932 are here reported.

The etiology, pathology and treatment of this condition are discussed.

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TYPHOID ABSCESS OF THE BREAST.

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As typhoid fever becomes more infrequent, its complications and sequelæ occur correspondingly rarely and one of the rarest complications, mastitis, is more or less a curiosity. Mastitis usually develops at the close of typhoid fever or during convalescence, and is bilateral in about half the cases according to McCrae¹ and in about one-third according to Madelung.² It is a mild and minor complication. It may occur in males though this is very unusual according to most writers. However, it was present in 1 male out of 4 cases observed by McCrae,¹ and Curschmann³ mentions 2 examples of slight mastitis in males.

As to frequency, Berg⁴ reported 4 instances among 1626 cases of typhoid fever; Schultze⁵ found 2 cases in 2580 typhoid fever patients, and McCrae¹ noted 4 cases of mastitis (2 suppurative) in a series of 1500 typhoid patients. The *Index Medicus*, from 1924 to 1931, inclusive, lists only 2 reports of typhoid mastitis or abscess, 1 case by Snoke and Goforth⁶ (1926) and a report of 2 cases by Cattaneo.⁷ Madelung² reviewed the matter in 1917 and found 30 cases, 26 of which he considered authentic. Suppuration in typhoid mastitis is rare according to Cattaneo,⁷ though McCrae¹ states that it develops in half the cases. When pus does form, the typhoid bacillus has not always been sought or found. In Madelung's² 30 cases bacteriologic examinations were made in only 7 patients. In 2 of these the typhoid bacillus was not recovered, in 2 others it was found along with the staphylococcus and in 3 cases it was found in pure culture. In Snoke and Goforth's⁶ case the typhoid bacillus was cultured from the pus of the amputated breast and later from the wound. The organism was cultured from that 1 of Cattaneo's⁷ 2 cases which showed bilateral involvement by squeezing a little

seropus from the left nipple, after punctures of the breasts had failed.

The case herewith reported gave conclusive bacteriologic evidence of the condition, and occurred, which is unusual, in a virgin breast. It is also worthy of note that while the early blood culture was positive, the many agglutination tests and cultures of urine and feces were negative up to the time of the abscess formation. In this respect the case resembles that of Snoke and Goforth,⁶ which had an early positive blood culture but repeated negative Widal's and feces cultures. The possible method of infection, mentioned in the history, is also worthy of consideration.

Report of Case.—S. M., white, female, aged 22 years, single, telephone operator, was admitted to the Hahnemann Hospital, March 14, 2 weeks after a visit to a seashore resort. Her symptoms were general and vague, the most specific being a dry cough and slight headache. She remained in the hospital 1 month, at the end of which time no conclusive diagnosis was reached, though numerous physical, laboratory and roentgenologic examinations were made. During the month the temperature ranged from 98° or lower in the morning to 99° F. at night, and the 2 days before her discharge her temperature was normal. Sputum and tuberculin tests were negative. There was no anemia and the leukocyte count was 7000. A typhoid agglutination test was not done. During her stay in the hospital she was visited by a woman friend whose sister was at that time ill in the hospital with typhoid fever. This incident may have some significance because this woman and another sister were later admitted to the hospital with typhoid fever. That is, 3 sisters (one of them the previous visitor) were sick in the hospital with typhoid fever and 1 of them died.

After her discharge the patient remained home for 10 days, during which time her general feeling of illness increased and she developed a constant severe headache. She was readmitted to the hospital April 25 with a temperature of 104°. Her fever continued between 103° and 104° for a week, after which it gradually dropped during the second week to 102°, where it remained for the third week. After this it slowly approached normal, which was reached on May 21. During the febrile period and especially in the earlier part, the patient was markedly toxic. The leukocyte count on the first 4 days of the second admission averaged 5000. Typhoid and paratyphoid agglutination tests were done April 27 and 28, May 11 and 19 and June 7; and were all negative. But a blood culture taken April 27 showed a pure growth of typhoid bacillus. During May, numerous cultures of stool and urine were negative for typhoid. The agglutination test for undulant fever was negative. Urinalyses showed nothing but occasional albuminuria. Another blood culture on May 17 was negative for typhoid. On account of the numerous negative agglutination tests and the negative cultures of stool and urine the clinicians were inclined to look askance at the diagnosis of typhoid fever in spite of the early single positive blood culture.

After the temperature reached normal on May 21, it remained so for a week and the patient seemed convalescent. On and after May 28 the temperature showed a slight rise evening to between 99° and 100° and on June 4, the patient first complained of a small, markedly tender, indurated focus in the upper, outer quadrant of the left breast. This tenderness remained, the induration increased and in 2 weeks the part became reddened and plainly suggested suppuration. On June 19 the abscess was incised and drained thick, yellow creamy pus. Spreads and cultures were made at once. The spread showed numerous pus cells but no bacteria. The culture

in 24 hours showed a short, Gram-negative motile bacillus. This organism fermented glucose with acid but no gas formation and formed neither acid nor gas with lactose. The organism was strongly agglutinated by the patient's serum in a dilution of 1 to 200 and also in the same dilution by a positive typhoid serum. The identification of the organism as a typhoid bacillus was therefore regarded as satisfactory. The patient's serum at this time (May 18) also agglutinated stock typhoid bouillon cultures. Following the opening of the abscess it rapidly healed and further cultures from the wound were negative. The patient left the hospital apparently well on July 5.

Summary. A case of typhoid mastitis in a virgin breast terminated in suppuration, and from the pus the typhoid bacillus was obtained in pure culture. The rarity of the condition is discussed.

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REVIEWS.

LES POISONS DU BACILLE TUBERCULEUX ET LES RÉACTIONS CELLULAIRES ET HUMORALES DANS LA TUBERCULOSE. By DR. JEAN ALBERT-WEIL, Chef de Clinique Médicale adjoint à la Faculté de médecine de Strasbourg, Ancien Interne des Hopitaux de Strasbourg. Preface by Professeur A. Borrel. Pp. 327; 6 illustrations. Paris: J.-B. Bailliére et Fils, 1931.

THIS book is to a great extent a compilation of the studies of a number of American investigators on the chemical composition of the tubercle bacillus and the biologic reactions induced by the different chemical fractions. The four main divisions deal with the chemistry of the tubercle bacillus, the antigenic nature of the various fractions and the cellular reactions in tuberculosis, the biologic action of the various fractions, and the general conception of the pathogenesis of tuberculosis. The author has simplified the subject matter by the introduction of several tables, which summarize respectively the method of preparation and the biologic action of the various chemical fractions of the tubercle bacillus. The fact is stressed that the newer knowledge of the chemistry and action of the fractions of the tubercle bacillus are based on cultures grown on media of known chemical composition.

J. A.

CLINICAL ENDOCRINOLOGY OF THE FEMALE. By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and LEOPOLD GOLDSTEIN, M.D., Demonstrator of Obstetrics, Jefferson Medical College, etc. Pp. 519; 117 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.00.

IN this book the authors have correlated their laboratory and clinical investigations of alterations in the function of the several glands of internal secretion. They have also included a comprehensive, yet critical, review of the many outstanding discoveries of recent years in this field. This monograph, the result of their labor, gives us an understanding of the present-day conception of the subject.

One by one the various glands have been taken up with a thorough consideration of the recent ideas of their physiology, complex inter-relationships, alterations and diagnosis of dysfunctions.

The subject of menstruation, the disorders of this phenomenon and the therapy of such disorders, forms a very large and interesting section of the book. It is introduced by a consideration of the blood tests for the various hormones. The authors are evidently convinced, in opposition to the view of Zondek and others, of the individuality of the anterior pituitary hormone. The contrast in the etiology of functional bleeding at puberty and at the menopause is clearly brought out. It cannot be said that any overenthusiasm for commercial biologic preparations characterizes the chapter on therapy. The indications for the potent and easily available anterior pituitary hormone are given. The authors are justly cautious in their discussion of low dosage irradiation of the pituitary and ovary.

The hormonal aspects of sterility, pregnancy, parturition, and lactation summarize concisely recent theories and experiments, and their clinical application. The outstanding practical laboratory procedure of this new work, the diagnosis of pregnancy by the use of test animals, is offered in detail, in its various modifications, as a guide to technicians. Two beautiful colored plates by McNett are found here.

This is an excellent book in a comparatively new field of medicine and will stand as a present measure of what has been recently learned, while the authors and others continue their investigations.

A final remark must note the voluminous bibliographical index and references indicative of the close scrutiny which the authors have made of the literature.

P. W.

THE CHEMISTRY OF TUBERCULOSIS. By H. GIDEON WELLS, M.D., PH.D., Director of the Otho S. A. Sprague Memorial Institute, and Professor of Pathology in the University of Chicago, and ESMOND R. LONG, M.D., PH.D., Director of the Laboratory of The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, and Professor of Pathology, University of Pennsylvania, formerly Professor of Pathology in the University of Chicago. Pp. 481; illustrated with tables. Second edition thoroughly revised. Baltimore: The Williams & Wilkins Company, 1932. Price, \$7.00.

THE progress of research in tuberculosis, and especially with mycobacteria, since the first edition of this book has necessitated extensive revision or expansion. This is particularly true of the section on "the chemistry for acid-fast bacteria." The fruitful research stimulated in this field by the National Tuberculosis Association is thoroughly discussed and reviewed.

The book is truly "a compilation and critical review of existing knowledge on the chemistry of the tubercle bacillus and its products, the chemical processes in the host, and the chemical aspects of the treatment of tuberculosis."

This edition is carefully arranged and clearly written, and will continue to be a valuable reference work to those engaged in laboratory studies on mycobacteria, or concerned in the treatment of tuberculosis.

H. R.

THE USE OF LIPIODOL. By J. A. SICARD, Late Professor in the Faculty of Medicine, Paris, and Physician at the Necker Hospital, and J. FORESTIER (Aix-les-Bains). Pp. 235; 50 illustrations. New York: Oxford University Press, 1932. Price, \$4.00.

AN excellent authoritative treatise by the men who have been the pioneers in the development of iodized oil for diagnostic and therapeutic purposes. This book is short and concise, yet comprehensive, bringing together for the first time the varied applications of lipiodol as an aid in diagnosis. It deals with lipiododiagnosis in the central nervous system, the bronchopulmonary system, male and female generative organs, urinary tract, blood-vessels, abscesses and sinuses, the paranasal sinuses, lacrymal ducts, miscellaneous applications and the estimation of secretory activity of the stomach. In the concluding chapter lipiodotherapy is discussed. There is a lengthy bibliography devoted primarily to foreign references. The illustrations are excellent. Recognizing the importance of proper technique in the successful use of lipiodol, special emphasis is placed upon this aspect of the subject. This book will be of considerable value to the various specialists who have occasion to use lipiodol but will be of greatest benefit to the radiologist whose necessary interest in all branches of medical practise makes it essential that he have a ready reference work on this important adjunct to his art.

K. K.

A DESCRIPTIVE ATLAS OF RADIOGRAPHS. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S.ED. Second edition, revised and enlarged. Pp. 552; 767 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$3.50.

THIS book is primarily intended for the clinician; the radiologist will find it of little value. It consists of a collection of roentgenograms showing the diversified conditions in which the Roentgen ray may be of value in diagnosis. Each roentgenogram is accompanied by a short descriptive note which states in a concise manner the essential features depicted in the radiograph. No attempt is made to teach roentgenologic interpretation. Great care has been exercised in the selection of material and the illustrations made therefrom are excellent. One cannot help but be impressed by the enormous rôle that radiology is playing in the practise of modern medicine. This fact, which is well established in this volume, appears to be the sole purpose of this work. K. K.

FUNCTIONAL DISTURBANCES OF THE HEART. By HARLOW BROOKS, M.D., Attending Physician, Fourth Medical Service, Bellevue Hospital, etc. Pp. 288. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.

THE book presents the personal observations of the author "during many active years of practice." It deals primarily with "the methods which have proven themselves useful in his experience, both in the recognition and in the treatment" of functional disorders of the heart. It is designed to "give, for the assistance of other practitioners, the fruit of his years of clinical study of these problems."

A book of this type usually contains a certain number of statements which may not be entirely scientifically proven or even have the major weight of the evidence in opposition. However, the clinical descriptions and the advice as to management of these patients will doubtless be helpful to practitioners of medicine. The author's wide experience makes him eminently capable of understanding the psychologic aspects of these disorders. F. W.

THE CARDIAC OUTPUT OF MAN IN HEALTH AND DISEASE. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Physiology in the Medical School of the Johns Hopkins University. Pp. 325; 14 illustrations and 57 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.00.

THIS monograph, the first to cover this very active field of research, contains a detailed description of the author's methods and a critical review of the literature, the completeness of which is attested by the 483 titles in the bibliography. Thus an account is given of the normal physiologic variations in the cardiac output and of the effect of drugs and physical therapeutic measures. The findings in certain types of cardiac disease are also given.

The author believes that his method will accurately measure the cardiac output of man under most conditions, and its results, as well as those obtained by other methods, are discussed from this point of view. Whether the method is as accurate as the author believes might well be debated. In any event, the book will prove most useful for workers in this field, and to clinicians interested in circulatory physiology. Nothing of immediate practical value has as yet been derived from these studies. I. S., Jr.

PROSPECTING FOR HEAVEN. By EDWIN R. EMBREE. Pp. 185. New York: The Viking Press, 1932. Price, \$1.75.

IN the novel guise of four evening conversations between eight interlocutors, this book entertainingly presents a collective opinion as to what may be expected of the "Mental Sciences" in harnessing the tremendous material now at our disposal "for the creation of a possible heaven on earth." In addition to the editor and a mythical Chinese philosopher, the talkers are C. M. Hincks, an internationally known psychiatrist, Victor Heiser, the sanitarian, Charles Judd and Franz Alexander, psychologists, and Howard Odum and Margaret Sargent, sociologists. While the conversations obviously did not take place as recorded, the contributors have certificated that they convey accurately "some at least of our ideas as to possible scientific steps to the good life." The skillful weaving into conversational form—a sort of semiscientific Heptameron—of descriptions of the evolution of the mind, chief types of insanity, principles of psychoanalysis, "tools of wisdom," the art of living together, and various "cross-roads to heaven" must be read in full to be appreciated. Neither can the various constructive suggestions even be indicated here. Stimulation to further thought as well as a measure of satisfaction toward the reconciliation of scientific progress with human limitations may be guaranteed to the reader.

E. K.

HANDBOOK OF THE VACCINE TREATMENT OF CHRONIC RHEUMATIC DISEASES. By H. WARREN CROWE, D.M., B.Ch. (OXON.), M.R.C.S., L.R.C.P., Director of the Charterhouse Rheumatism Clinic, etc. Pp. 79. Second edition. New York: Oxford University Press, 1932. Price, 80c.

DURING the 2 years since the first edition of this handbook appeared, the author's methods have been modified by further reductions in dosage, bringing the initial dosage at times as low as 100 bacteria. There is abundant evidence in the author's experience to indicate that the range of dosage, seldom above 10 million bacteria, is more efficient than larger doses. These doses elicit reaction phases in arthritis ("Reaction, Response and Relapse") such as do not appear following the larger ones. The first, an aggravation of symptoms within the first 48 hours, is detrimental and to be avoided by suitable further reductions in dosage. The second is the desired alleviation of symptoms and promptly follows a suitable dosage. The third, a return of symptoms after a period of relief, indicates that the dosage must be repeated.

These *reaction* phases, their interpretation, and the ultimate results of treatment are identical with those appearing after the injection of water-soluble extracts of single strains of streptococci in even smaller doses, as developed independently in this country in the treatment of chronic arthritis. This weakens the author's argument for the specificity in a particular patient of at least one of the 155 strains of streptococci entering into his polyvalent vaccine. With doses of 100 bacteria from a polyvalent vaccine containing 155 strains, on a pure mathematical basis, one could not expect to have included in each dose even a single bacterium of the one or several strains specific in a given patient. Constancy of clinical responses with such doses argues against specificity of strain, or in favor of the essential elements being contained in solution in the menstruum suspending the bacteria.

A recognized handicap in the treatment of arthritis with vaccines is the possibility of increasing a patient's reactivity to it. This contingency may depend upon the author's use of subcutaneous rather than intravenous

injection. It does not occur after subcutaneous injections if doses sufficiently small are employed, but these can be obtained only through the use of soluble extracts.

This handbook should be studied by every physician who uses products of streptococci in the treatment of chronic arthritis. The use of minute dosage, the recognition of the three phases of reaction and the interpretation of them as presented in this handbook will assure a measure of success heretofore unobtained in the treatment of atrophic and hypertrophic arthritis.

J. S.

BIRTH, STILLBIRTH AND INFANT MORTALITY STATISTICS FOR THE BIRTH REGISTRATION AREA OF THE UNITED STATES, 1929. Fifteenth Annual Report. Pp. 373; illustrated with tables. Washington: United States Department of Commerce, Bureau of the Census, 1932.

ORDINARILY such compilations as these are of little interest to the average individual, but the fact that the present report marks the last year in which there was an increase in births over deaths in the United States will make this collection of statistics stand out as a prominent marker in our biologic history. From this time on it is probable that natality will barely balance mortality. The equilibrium seems to have been reached from 30 to 50 years prior to the time of its predicted arrival. It is to be hoped that the deep significance of the figures presented here will be made evident to the medical public in a more digestible form in the hope that the number of stillbirths may be decreased and the infant mortality rate lowered.

P. W.

LABORATORY SERVICE AND THE GENERAL PRACTITIONER. By ARNOLD RENSHAW, M.D., B.S. (LOND.), D.P.H. (MANC. AND CAMB.), Director of the Laboratory of Applied Pathology and Preventive Medicine, Manchester, etc. With an Introduction by DAN MCKENZIE, M.D. (GLAS.), F.R.C.S.E. Pp. 267; 8 illustrations. New York: Oxford University Press, 1932. Price, \$2.50.

As a clinical pathologist, the author has experienced a need of a closer relationship between the clinician and the laboratory service following the rapid growth of this phase of pathology in modern medicine. The common clinical conditions are listed, each accompanied by a plan of investigation which should be undertaken to bring out the diagnosis. The helpful features of the book are the systematic manner in which the conditions are approached and the correlation of the physical characters of certain specimens with objective pathologic findings. The latter phase, however, is very briefly covered. The interpretations of the tests for diagnosis with discussions are also brief. The book does not contain any details of technique. It is, however, useful as a guide for the clinician in setting out a plan of investigation of a clinical condition with an interpretation of the results.

J. B.

EXCITABILITY—A CARDIAC STUDY. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 208; 15 illustrations. New York: Oxford University Press, 1932. Price, \$3.85.
A NEW PHYSIOLOGY OF SENSATION. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 70. New York: Oxford University Press, 1932.

THESE two books attempt to present as a whole the author's work on cardiac muscle and to relate it to more general principles; over half of the

references made are consequently to the author's own work. While his contention, that experiments on enfeebled hearts with solutions far removed from those usually considered advisable are not only justifiable but illuminating, is warranted, any illumination provided proceeds from his facts rather than from their presentation. Our concept of excitation is not assisted by such a statement as "Muscle and nerve contain two sources of potential energy, the kinesiphores, which are the potentialities of a salt-colloidal system. The two kinesiphores are calcium and . . . fineness of colloidal state with adequate salt adsorption." But one cannot complain that he is limited by orthodoxy; for instance, he states "It may be that the T wave represents, in part at least, antidromic impulses passing by nervous paths from ventricle to pacemaker." The review of experimental evidence in the first book may have some value. Language may be a means of clarifying thought or of submerging facts in a vast pile of terminology, and the scientist is too apt to be betrayed into the second usage; these books might provide a warning of this danger.

H. B.

BOOKS RECEIVED.

NEW BOOKS.

Publications of the Committee on the Costs of Medical Care. No. 21. Organized Medical Service at Fort Benning, Georgia. By I. S. FALK, PH.D. With Reports on Certain Phases of the Organization by DAVID RIESMAN, M.D., Sc.D., and GEORGE P. MULLER, M.D. Pp. 119; 2 illustrations and various tables. Price, 90 cents. No. 23. *Surveys of the Medical Facilities in Three Representative Southern Counties.* By C. ST. C. GUILD, M.D., DR.P.H. With a Statistical Appendix on the Method of Selecting Representative Counties by I. S. FALK, PH.D. Pp. 172; 9 illustrations and various tables. Price, \$1.00. No. 24. *The Incomes of Physicians. An Economic and Statistical Analysis.* By MAURICE LEVEN, PH.D. Pp. 135; 20 illustrations and various tables. Price, \$2.00. Chicago: The University of Chicago Press, 1932.

The Tides of Life. The Endocrine Glands in Bodily Adjustment. By R. G. HOSKINS, PH.D., M.D., Director of Research, Memorial Foundation for Neuro-endocrine Research; Research Associate in Physiology, Harvard Medical School. Pp. 352; illustrated. New York: W. W. Norton & Co., Inc., 1933. Price, \$3.50.

The Department of State Conference Series No. 12. Sixth International Congress of Military Medicine and Pharmacy and Meetings of the Permanent Committee. The Hague, Netherlands, June, 1931. Report of COMMANDER WILLIAM SEAMAN BAINBRIDGE, M.C.-F., U.S.N.R., for the Delegation from the United States of America. Pp. 167; 1 illustration. Washington: United States Government Printing Office, 1933. Price, \$1.00 (cloth).

Endocrine Medicine, Vol. IV. Bibliography, Indexes of Names and Subjects. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Staff, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine. Pp. 117. Springfield, Ill.: Charles C Thomas, 1932.

- A List of Writings on the Cardiovascular System Exhibited During the Graduate Fortnight of the New York Academy of Medicine, 1931.* Arranged by DR. CHARLES K. FRIEDBERG, and the Staff of the Library. Pp. 93. New York: New York Academy of Medicine, 1932.
- The Surgical Clinics of North America, Vol. 13, No. 1 (Pacific Coast Surgical Association Number—February, 1933).* Pp. 247; 90 illustrations. Philadelphia: W. B. Saunders Company, 1933.
- Hoerber's Surgical Monographs. The Duodenum.* Its Structure & Function; Its Diseases & Their Medical & Surgical Treatment. By EDWARD L. KELLOGG, M.D., F.A.C.S., Professor of Surgery and formerly Professor of Gastroenterology, New York Polyclinic Medical School, etc. With a Foreword by GEORGE DAVID STEWART, M.D., F.A.C.S., New York. Chapter on Duodenal Parasites by BAILEY K. ASHFORD, M.D., Sc.D., Professor of Tropical Medicine and Mycology, University of Porto Rico and Columbia University, New York, etc. Section on X-ray Diagnosis by A. JUDSON QUIMBY, M.D., Professor of Roentgenology, New York Polyclinic Medical School. Pp. 855; 287 illustrations, 3 in color. New York: Paul B. Hoeber, Inc., 1933. Price, \$10.00.
- Syllabus of Medical History.* By VICTOR ROBINSON, M.D., Professor of History of Medicine, Temple University School of Medicine, Philadelphia. Pp. 110; illustrated. New York: Froben Press, Inc., 1933.
- The Gold-headed Cane.* By WILLIAM MACMICHAEL, M.D.; Edited with Explanatory and Illustrative Notes and an Essay on William MACMICHAEL, M.D., his Life, his Works and his Editors, by HERBERT SPENCER ROBINSON. Pp. 223; illustrated. New York: Froben Press, Inc., 1932. Price, \$3.50.
- Clinical Physiology of the Eye.* By FRANCIS HEED ADLER, M.A., M.D., F.A.C.S., Instructor of Physiology and Ophthalmology, Medical School, University of Pennsylvania; Assistant Surgeon, Wills Hospital. Pp. 406; 92 illustrations. New York: The Macmillan Company, 1933. Price, \$5.00.
- A Critique of Sublimation in Males.* A Study of Forty Superior Single Men. By W. S. TAYLOR, Professor of Psychology, Smith College. Pp. 115. Worcester, Mass.: Clark University Press, Genetic Psychology Monographs, 1933. Price, \$2.00.
- Abstract of Publication No. 23. Surveys of the Medical Facilities in Three Representative Southern Counties.* By C. ST. C. GUILD, M.D., DR.P.H. Pp. 14; 3 tables. *Abstract of Publication No. 25. The Ability to Pay for Medical Care.* By LOUIS S. REED, PH.D. Pp. 15; 3 tables. Washington, D. C.: The Committee on the Costs of Medical Care, 1932-1933.
- Diseases of the Heart.* By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., HON.D.Sc. (MICHIGAN), Physician in Charge of Department of Clinical Research, University College Hospital, London, etc. Pp. 297; 44 illustrations. New York: The Macmillan Company, 1933. Price, \$3.50.
- Clinical Diagnosis, Physical and Differential.* By NEUTON S. STERN, A.B., M.D. (HARVARD), Associate Professor of Medicine, University of Tennessee School of Medicine, Memphis. Pp. 364. New York: The Macmillan Company, 1933. Price, \$3.50.

NEW EDITION.

- Criteria for the Classification and Diagnosis of Heart Disease.* By the Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, Inc., HAROLD E. B. PARDEE, M.D., Chairman. Pp. 131; 28 illustrations and 48 electrocardiograms. Third edition. New York: New York Tuberculosis and Health Association, 1932. Price, \$1.00.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Studies in the Experimental Production of Simple Goiter.—WEBSTER (*Endocrinol.*, 1932, 16, 617) recounts the sequence of events that have led up to the knowledge that there are certain food substances which, given to the experimental animal, are capable of producing goiter. Succinctly, it was noted in the course of some studies of experimental syphilis at the Johns Hopkins Medical School that some rabbits were developing a goiter when they were on a stock diet of 200 gm. of cabbage daily plus 50 gm. of hay and 50 gm. of oats once a week. Practically 100 per cent of the rabbits who were in the laboratory for over 40 days developed thyroid glands which were much above the normal weight. It became apparent that cabbage was the responsible factor for the production of these goiters. If the rabbits were fed hay and oats the thyroid enlargement did not appear. Control experiments were carried out to see if it was possible that other factors played a rôle in the production of the goiters. It was found, moreover, that the addition of 7.5 mg. of iodine to the goitrogenous diet protected rabbits for over a year at least. The animals developed goiter in direct relationship to the duration of the feeding experiment, the degree of hyperplasia running level with the duration of the diet. It was noted that goiters were more easily produced in winter than in summer. It was believed that iodine lack might have some bearing upon the cabbages, but the goitrogenic agent was found to be much more powerful than the iodine deficiency. Other vegetables, such as Brussels sprouts and cauliflower, were likewise found to be goitrogenic. There are certain mechanical ways of treating cabbage to increase or decrease its goiter-producing power. These studies indicate a method whereby it is possible to produce goiter experimentally and open a field in which pathologic goiters may be controlled. The general summary of the author points out that the goitrogenic substance is probably a cyanide which produces a depression of tissue oxidation. Compensation is brought about by the overproduction of the activator of overproduction, thyroxine, which in turn brings about a relative iodine insufficiency with subsequent hyperplasia of the thyroid. Further investigation in the cause of goiter, it is suggested by the author, must be directed toward discovering the inherent disturbance in the animal organism which is capable of producing a relative iodine insufficiency.

The Extracardiac Anastomoses of the Coronary Arteries.—In a series of experiments that were carried out by HUDSON, MORITZ and WEARN (*J. Exp. Med.*, 1932, 56, 919), a colloidal suspension of carbon particles was injected into the coronary arteries of human hearts removed at autopsy. In most instances the method found satisfactory was to remove the thoracic organs, the diaphragm and the abdominal viscera together, particular care being taken to keep the pericardium intact around the great veins. A 3 per cent solution of lamp black and 5 per cent acacia was then injected and the specimen placed in 10 per cent formalin for 24 hours. Thirty-one specimens in all were studied. It was found that there were extensive anastomoses of the auricular branches and the coronary branches to the pericardial fat with the pericardiophrenic branches of the internal mammary arteries and the mediastinal, pericardial and other branches of the aorta. Between the cardiac and the extracardiac vessels around the ostium of the pulmonary veins were most extensive anastomoses. The injection mass could be demonstrated to have passed not only from the coronary arteries and into the vessels of certain structures, but it was also possible to demonstrate heart vessels injected from the thoracic branches of the aorta. The authors believe that this rich potential extracardiac coronary collateral circulation may be significant in compensating for sclerotic changes in the larger branches of the coronary arteries.

Precocious Development of Sexual Characters in the Fowl by Daily Injections of Hebin.—These reports of DOMM and VAN DYKE (*Proc. Soc. Exp. Biol. and Med.*, 1932, 30, 349) deal with the effect of the daily administration of hebin, a purified gonad-stimulating hormone prepared from sheep pituitary glands. In the first report the preparation was given to light brown Leghorn cocks and their juvenile sex character changes were studied largely by the head furnishings, which were measured at regular intervals. The treated cocks remained in good physical condition despite the daily injections of from 4 to 32 rat units over a period of 14 to 36 days. The first effect observed occurred in some instances as early as 48 hours after injections began, as a pronounced stimulation of head furnishings. These began rapidly to increase in size and the young cocks soon were attempting to crow. The autopsies revealed hypertrophy of the testes in the treated individuals, which were larger and heavier than in the untreated birds. The thyroid glands were likewise larger and heavier. Other organs did not show any significant change, but distinct histologic modifications were found in the testes of the experimental birds. These observations confirmed Domm's previous work. It is assumed that the injected gonad-stimulating hormone acted directly on the thyroids and gonads and that the precocious development of the testes accounts for the development of other sexual characters. In the second paper, which has to do with the female bird (p. 351) there is noted likewise the phenomenal growth of head furnishings together with the considerable hypertrophy of the ovaries as contrasted with the controls. Here again the thyroid showed perceptible hypertrophy. It is assumed that the injected gonad-stimulating hormone in the stimulation of the gonads brought about a precocious endocrine, rather than gametogenetic, functioning responsible for the development of the other sexual characteristics.

SURGERY

UNDER THE CHARGE OF

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Serum Amylase and the Diagnosis of Pancreatic Disease.—Diseases of the pancreas, other than diabetes, are counted among the most difficult of the abdominal diseases from the standpoint of diagnosis. In an attempt to diagnose surgical lesions of the pancreas more accurately, a variety of laboratory tests have been proposed only later to be discarded. Several decades ago CAMMIDGE (*Lancet*, 1904, 1, 782) reported a test which was supposed to give accurate evidence of disease of that portion of the gland having to do with its external secretions. It was used extensively at the time but now is of purely historical interest. Numerous investigators have attempted to study the enzymes present in the duodenum as a means of determining the pancreatic function. The difficulties of such studies are evident and, as would be expected, they have not been of any real value in diagnosis.

In 1846 MAGENDIE (*Gaz. méd. de Paris*, 1846, 1, 734) demonstrated the presence of amylase in the blood serum. Since then many attempts have been made to correlate the amount of this enzyme in the blood in various diseases of the pancreas. Since the enzyme is excreted in the urine, attempts have been made to study the urinary amylase for a similar purpose.

During the past few years several attempts have been made to determine, under optimum conditions, whether serum amylase studies are of diagnostic value in differentiating surgical disease in the upper abdomen. DAVISON (*Bull. Johns Hopkins Hosp.*, 1925, 37, 281) has published a method for the determination of serum amylase activity which has been used either as originally described, or with modifications by several groups of workers.

The work of Elman and Graham in this field marked the first serious attempt by surgical investigators to enter this very important field. ELMAN, ARNESON and GRAHAM (*Arch. Surg.*, 1929, 19, 943) and ELMAN (*Arch. Int. Med.*, 1931, 48, 828) have studied the amount of amylase in the serum in patients and have correlated the data which they obtained with the findings at operation or autopsy. They concluded that the determination of the serum amylase is of undoubted value in determining the presence of suspected pancreatic disease. Shortly after Elman's first paper, WAKEFIELD, McCAUGHAN and McVICAR (*Arch. Int. Med.*, 1930, 45, 473) published a similar study using similar methods (ELMAN and McCAUGHAN, *Arch. Int. Med.*, 1927, 40, 58) for the determination of the serum amylase, and came to nearly opposite conclusions, in that they could find no correlation between the serum amylase content and the extent of the disease of the pancreas.

POPPER and SELINGER (*Wien. klin. Wchnschr.*, 1928, 41, 199), POPPER (*Deutsch. med. Wchnschr.*, 1929, 55, 1712) and POLACCO and PECCO

(*Klin. Wchnschr.*, 1928, 7, 1867) have published similar studies in the European literature. The first authors found the determination of serum amylase of some value in making a diagnosis of pancreatic dysfunction. Popper, however, found an increase in the blood amylase after gastric resection which he believed may have been due to injury to the pancreas during the operation, since the amylase value returned to normal within a few days. Polacco and Pecco found an increase in the serum amylase in 32 per cent of patients with gastric or duodenal ulcer and in 42 per cent of patients with acute biliary tract disease.

The difficulties encountered in evaluating such studies is evident from the fact that the same type of study has been used as a test of kidney function by HARRISON and LAWRENCE (*Lancet*, 1923, 1, 169), REID (*Brit. J. Exp. Path.*, 1925, 6, 314) and others. In the presence of severe renal disease the serum amylase is increased. Furthermore, MOECKAL and ROST (*Ztschr. Physiol. Chem.*, 1910, 67, 433) reported an increase in the diastatic activity of serum in diabetes mellitus. More recently, REID and MYERS (*J. Biol. Chem.*, 1933, 99, 607) have confirmed these observations.

If the clinical interpretations of serum amylase determinations are involved and difficult to evaluate, the results obtained from experimental animals are no less confusing. MILNE and PETERS (*J. Med. Res.*, 1912, 26, 415) and others have found that pancreatectomy causes an increase in the serum amylase, while REID and NARAYANA (*Quart. J. Exp. Physiol.*, 1930, 20, 305) found little or no change, and OTTEN and GALLOWAY (*Am. J. Physiol.*, 1910, 26, 347) found that pancreatectomy caused a fall in the serum amylase. Recently, ZUCKER, NEWBURGER and BERG (*Am. J. Physiol.*, 1932, 92, 209) and REID, QUIGLEY and MYERS (*J. Biol. Chem.*, 1933, 99, 615) have confirmed the findings of Otten and Galloway. Ligation of the pancreatic ducts causes a sudden and marked increase of the serum amylase according to JOHNSON and WIES (*J. Exp. Med.*, 1932, 55, 505), Zucker, Newburger and Berg, and Wolff and Holt (unpublished data from this laboratory). This increase persists for only a few days and is then followed by a period in which the serum amylase values are below those present previous to ligation of the duct. Zucker, Newburger and Berg, in contrast to the results of Elman and McCaughan found that drainage of the pancreatic ducts results in similar changes to those found after ligation of the pancreatic ducts.

There is no doubt from the extensive data in the literature that the amount of serum amylase varies coincident with pathologic changes in the pancreas. Since the serum amylase following pancreatic duct obstruction may be increased, decreased or normal, depending on the length of time which has elapsed following the onset of the obstruction, it is difficult to see how single determinations will give a clear picture of the changes occurring in the pancreas. However, a normal blood diastase which remains normal for several days would tend to exclude the pancreas. Surely, in those cases in which serum amylase determinations are made as an aid to diagnosis, the interpretation must be made in the light of other findings. As a test of disease of the pancreas it has not proven to be specific. Further studies along the line of those made by Elman and his co-workers may throw additional light on the subject.

THERAPEUTICS

 UNDER THE CHARGE OF

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The Treatment of Myasthenia Pseudoparalytica With Glycocoll.—REMEN (*Deutsch. med. Wchnschr.*, 1932, 58, 889) presents a very brief note recording the favorable effects observed by him in 2 patients to whom oral daily doses of 10 gm. of glycocoll were administered continuously for periods of 2 months or more. The treatment is based upon the fact that glycocoll is capable of restoring to normal the disturbed creatin-creatinin metabolism which has been determined to exist in these patients, who are commonly observed to have an elevated creatinuria. In both of the author's patients the treatment relieved the pronounced tendency toward fatigue and gradually tended to restore the function of the patients' muscles. One patient who had been scarcely able to walk at all for 6 months so far regained his strength as to be able to walk and to climb stairs without difficulty. Both an existing ptosis and diplopia disappeared and the myasthenic electrical reactions which had been present in practically all muscle groups also diminished or disappeared. The author feels that the results of this form of treatment are most promising and that it should be tried further despite its relatively high cost.

A New Treatment for Thrombosis.—Based upon the results of the modern study of the blood in relation to the tendency to the development of thrombosis, STUBER and LANG (*Deutsch. med. Wchnschr.*, 1932, 58, 885) have developed a therapy comprising the intravenous administration of germanin combined with an alkaline diet to which is added the daily administration of 40 gm. of neutral sodium citrate. Their own studies show that this combined form of treatment increases the rate of blood flow, overcomes an existing slowing of the flow, promptly alters the chemical and physical composition of the blood in the direction of increasing the ratio of albumin as compared to globulin and reduces the electrical charge of the blood cells together with the production of an increase in the alkali reserve. Each of these chemical and physical alterations is directly opposed to the conditions favoring thrombosis. The administration of germanin brings about an acute alteration while the alkaline diet and sodium citrate are administered for the purpose of maintaining the altered state. The authors find that to be effective the germanin must be administered intravenously. Their initial dose is 0.5 gm. and after 2 or 3 days subsequent doses of 1 gm. are given at intervals of 4 or 5 days. The only side action which they have observed from the administration of germanin is a transitory albuminuria. They believe that this plan of treatment is of thera-

peutic value in those patients who have already developed one or more thromboses as well as being of great value as a prophylactic. In cases of cardiac insufficiency they believe that adequate continued digitalis therapy is necessary and they recommend for cases of circulatory deficiency due to vasomotor depression, as in infectious diseases, the administration of camphor and caffeine as essential adjuvants.

Investigations on the Active Principles of Curcuma and the Action on the Secretion of Bile.—Supplementing and elaborating previous clinical studies of their own upon curcuma, KALK and NISSEN (*Deutsch. med. Wchnschr.*, 1932, 58, 1718) report the results of animal experiments and investigations upon man with extracts of curcuma, one representing the total extract of 10 gm. of the drug, the second only the ethereal oil contained in that quantity of the drug, and the third only the water-soluble constituents. Upon dogs they find that all three extracts markedly increase the flow of bile when administered through a duodenal tube. The whole extract, however, is more potent than either of the two fractions, although each of the fractions exhibits a considerable degree of activity. Comparative studies show the action of the whole extract of 10 gm. of curcuma to be somewhat less than that of 5 cc. of a 5 per cent solution of decholin given intravenously. The whole extract is dissolved in 150 cc. of hot water and administered directly into the duodenum by way of a duodenal tube. In every one of 24 investigations carried out on 13 patients this dose showed a pronounced increase in the flow of bile ranging from twice up to five times the previous flow. The biliary flow was accompanied by an increased elimination of bile pigment and the fixed constituents of the bile. The experiments seemed to show that the presence of the volatile oil in the extract contributes to its action by relaxing spasm of the biliary passages when present, and in two instances in man the repeated administrations of the total extract led to the spontaneous evacuation of a number of gall stones. The authors believe that the whole extract of curcuma constitutes a marked addition to our armamentarium for the treatment of many diseases of the biliary tract, especially those associated with diminished bile flows and that it is surpassed in its potency only by decholin.

Vaccine and Distilled Water Injections in the Treatment of Whooping Cough.—The conflicting evidence as to the therapeutic value of vaccine in whooping cough is briefly reviewed by BAYER (*Med. Klin.*, 1932, 28, 1459), to which he adds his own experiences confirming this conflicting evidence. In order to obtain more definite information he made comparative investigations upon two series of children, the one receiving vaccine, the other distilled water injections. The results showed that those receiving distilled water had more marked alleviation of symptoms and shorter duration of illness than those on vaccine treatment. The author explains this extraordinary difference between the two groups on the basis of differences in their composition and surroundings, which made the group receiving water much more susceptible to the influence of therapeutic suggestion. He believes, as a result of these experiences, that pertussis vaccine is without specific therapeutic value and that such benefit as may result from its use in individual cases is due solely to the therapeutic value of suggestion.

PEDIATRICS

UNDER THE CHARGE OF
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The So-called Allergic Manifestations and the Incidence of Respiratory Infections in Rheumatic and Non-Rheumatic Children.—McCLENN (Arch. Pediat., 1933, 50, 123) says that it has been shown repeatedly in rheumatic children that the so-called allergic manifestations are common and that often respiratory infections are responsible for the initial attacks and for the recurrence of the acute manifestations of the rheumatic infection. When the incidence of the so-called allergic manifestations associated with respiratory infections in 36 rheumatic patients, to the age at the development of the condition, were compared with 36 non-rheumatic patients of the same age and length of observation, it was found that the number and severity of the respiratory infections differed little in the rheumatic and the non-rheumatic groups. Repeated attacks of tonsillitis were observed in 88 per cent of the rheumatic and in 77 per cent of the non-rheumatic children. Acute follicular tonsillitis was observed in 47 per cent of the rheumatic and in 58 per cent of the non-rheumatic children. The so-called allergic phenomena were no greater in the rheumatic than in the non-rheumatic groups, with the possible exception of gastro-intestinal symptoms complicating respiratory infections, if this is an allergic manifestation. Acute suppurative otitis media occurred in 47 per cent of the rheumatic children and in 38 per cent of the non-rheumatic. Acute cervical adenitis occurred in 27 per cent of the rheumatic group and in 11 per cent of the non-rheumatic. Severe gastro-intestinal symptoms were associated with respiratory infections in 41.6 per cent of the rheumatic and in 19.4 per cent of the non-rheumatic cases. Twenty-two (61 per cent) of the rheumatic patients developed the condition before the tonsils and adenoids were removed and 14 (39 per cent) of them developed the condition after the operation. Of the control non-rheumatic patients, 23 (64 per cent) had the tonsils removed before the age of the development of the infection. Of the 14 rheumatic patients in whom the tonsils and adenoids were removed before the development of the rheumatic infection, 12 (86 per cent) developed signs and symptoms of a more or less chronic paranasal sinusitis.

Septicemia in the New-born.—DUNHAM (Am. J. Dis. Child., 1933, 45, 229) states that septicemia, in spite of the general impression to the contrary, is an important and relatively frequent cause of morbidity and mortality in the new-born. Blood cultures should always be taken when a new-born baby becomes ill and when the diagnosis is obscure. If the cause of the illness is determined early and transfusions of blood and other treatments are given, a number of these patients may be saved. There were observed 39 cases of septicemia in new-born infants occurring in a period of 5 years. The final diagnosis, based on the growth of organisms from the blood, was usually corroborated by clinical and, in many cases, by postmortem examination. The commonest organism found was the streptococcus, the staphylococcus and

the *B. coli*. Clinically, septicemia due to the streptococcus seemed to differ from other types of septicemia by the absence of jaundice and bleeding, by the less frequent enlargement of the spleen and by the more frequent appearance of cutaneous infections, omphalitis, peritonitis and meningitis. Streptococcus septicemia invariably terminated fatally. In the cases of septicemia caused by the staphylococcus and the *B. coli*, the jaundice was a common symptom, occurring in more than one-half of the cases in both groups. Bleeding was observed in about one-half of the cases in the staphylococcus group and in about one-third of the cases of the *B. coli* group. The spleen was frequently enlarged in both groups, in one-half or more of the cases. Anemia was less common in staphylococcus septicemia than in that caused by the streptococcus and *B. coli*. Infections of the urinary tract were found only in cases of *B. coli* septicemia. The staphylococcus and *B. coli* septicemias were not invariably fatal.

The Effectiveness of Commercial Diphtheria Toxoid in Active Immunization of Infants.—GREENGARD (*J. Am. Med. Assn.*, 1933, 100, 793) used 5 brands of toxoid, and 1 was noted to be definitely less effective than the other 4. In the first series of 28 cases, 4 (14.2 per cent) remained persistently positive. Of the 24 infants completely immunized, the interval between last dose of toxoid and the ensuing negative Schick test was over 6 weeks in 7 cases and as long as 20 weeks in 1. In this connection it must be borne in mind that, in an individual who has received a primary antigenic stimulus, even minute secondary antigenic stimuli, such as the very small amount of toxin used in a Schick test, may produce considerable amounts of antitoxin. It is, therefore, quite possible that some of the infants that became negative after 10, 12 or 20 weeks, may have responded to the repeated small doses of Schick toxin with sufficient antitoxin to bring them above the Schick level. In the second series on the less effective brand of toxoid, 6 of 30 infants (20 per cent) remained persistently positive. In this group all but 2 of the immunized infants demonstrated a negative Schick within 6 weeks of the second dose. The remaining groups showed definitely better results. Two groups showed 100 per cent protection and all but 1 of these cases showed the negative Schick within 6 weeks. Two other groups showed approximately 97 per cent immunized, and in these the immunity was demonstrated largely within 6 weeks. There was a natural error in observation due to the difference in developing immunity at different age periods. It was noted that the best results were developed in the older infants. This fact did not hold in the cases in the group using the brand of toxoid in which notably poor results eventuated, as the age group was the same as in two groups in which notably good results were observed. The age distribution of infants in whom the Schick test remained persistently positive is interesting. All but 1 of these 12 infants were under 6 months of age. This bears out the statements found in the literature, that young individuals form antibodies poorly. On the other hand, it is interesting to know that, with a potent toxoid, most infants under 6 months of age can be rendered Schick negative rapidly. The outstanding advantage of toxoid is that it may be of high antigenic potency, and it is non-toxic, irreversible and very resistant to changes in temperature, aging and the like.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Viosterol in the Treatment of Pemphigus.—LUDY and DE VALIN (*Urol. and Cut. Rec.*, 1932, p. 817) report the uncomplicated recovery of 6 cases of chronic pemphigus by the use of massive dosage of viosterol. They were led to the trial of this drug by the observation of the close connection between faulty nutrition and the incidence of chronic pemphigus, the disease for the most part occurring exclusively among the poorer classes, who live largely on ill-balanced diets, deficient in vitamins. The first case studied was a woman, aged 57 years, who had had for 2 months a widespread bullous eruption over the entire body, including the mouth. Viosterol was given in rapidly ascending doses up to 45 cc. daily, as well as ultraviolet irradiation pushed to the point of tolerance. Following a temporary state of mental aberration with sexual excitation, during which time the viosterol was discontinued the drug was again administered in doses of 12 cc. daily. Complete cure followed with no remissions the past 2 years of observation. All other cases studied were given doses of viosterol ranging from 4 cc. to 8 cc. three times daily. It is important to begin treatment the moment the diagnosis is established and the administration of adequate dosage pushed until the cessation of the eruption of new bullæ. Roentgen ray studies have shown no deposit of calcium in the soft tissues under this high dosage of viosterol. The blood calcium after 2 months' administration showed an average increase of 2 mg. per 100 cc. The authors comment on two known recoveries from pemphigus treated with viosterol in the practice of another physician and advocate the further trial of this method of treatment.

A Simplified Treatment of Ringworm of the Scalp.—BARKSDALE (*Med. J. and Rec.*, 1932, 136, 494) reports the results obtained in the treatment of 80 cases of tinea capitis by the local use of a 1 per cent bismuth violet (crystals) and 10 per cent salicylic acid in 70 per cent alcohol. The results were uniformly good in all coöperative patients, healing usually ensuing in from six to ten daily applications. Secondly infected cases require a longer course of treatment.

Erythema Nodosum in Undergraduate Nurses and Its Relationship to Tuberculosis.—CRUISE (*Canadian Med. Assn. J.*, 1932, 27, 603) champions the tuberculous etiology of erythema nodosum, a disease whose causation has periodically vacillated between those who favor either its rheumatic, tuberculous or specific bacillary background. The author has studied 33 pupil nurses with the disease and states

that one-third of the group subsequently developed definite or tentative tuberculous within a period of 6 months after the involution of the eruption. He states that erythema nodosum may be considered as much a manifestation of tuberculosis as pleurisy with effusion. The author suggests that in addition to a skiagram made during the acute phase of the eruption, it should be repeated in 3 months and every 6 months thereafter for a year or more.

Fatalities Due to Bismuth in the Treatment of Syphilis.—BEERMAN (*Arch. Dermat. and Syph.*, 1932, 26, 797) has reviewed the literature on fatalities due to bismuth used in the treatment of syphilis and has discovered 6 cases of sudden death and 17 of delayed deaths attributable to this cause. In all but one instance the sudden deaths followed the intravenous use of the drug and were associated with symptoms of colloidoclastic shock. The one sudden death following intramuscular injection was probably due to accidental intravascular deposition of the drug and reemphasizes the importance of pulling back on the plunger of the syringe to prevent this complication. Delayed deaths due to bismuth intoxication are usually attributable to involvement of the gastrointestinal tract, the liver or the kidneys or a combination of two or more of these structures.

GYNECOLOGY AND OBSTETRICS

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Artificial Vagina.—In those rare cases in which there is an absence of the vagina various methods of treatment have been advocated which belong into two major groups, namely, construction of a new vagina from plastic flaps of skin taken from the labia or thighs, or the implantation of some portion of the intestinal tract into the normal situation of the vagina. There is no clinic which has had a very extensive experience with any of these operations, but MASSON (*Am. J. Obst. and Gynec.*, 1932, 24, 583) believes that unless the new canal is lined with mucous membrane it will not be very satisfactory. He has operated upon 5 patients using the ileum and they are all well satisfied with the results. One of the objections to this operation is the high mortality rate, but he believes that if proper care is taken not to make undue tension on the loop of ileum, there should be no real risk from operation. The discharge which some of the patients complain of can be reduced by not making the loop any longer than necessary. In the occasional case it may not be possible to find a loop of ileum that can be brought down to the perineum, and in such event it will be advisable to use a loop of sigmoid or close the abdomen and use the ampulla of the rectum, but the risk is greater if the large bowel is used.

RADIOLOGY

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The Limitations of Physical Therapy in Otolaryngology.—In otologic practice FOWLER (*Arch. Phys. Therap., X-ray, Radium*, 1932, 13, 581) considers diathermy, ionization, Roentgen rays and ultraviolet rays as mostly of doubtful or negative value, except for certain surface lesions and for the symptom of pain, which symptom being a valuable clinical guide should not be thoughtlessly masked. Any man who claims to cure deafness, as such, by any therapeutic measure is deliberately or ignorantly confounding a symptom with disease, because deafness may result from many widely differing lesions requiring widely different managements.

Pitfalls in Tonsil Coagulation.—BARLOW (*Arch. Phys. Therap., X-ray, Radium*, 1932, 13, 598) feels that electrocoagulation of the faucial tonsil is now on a safe and sane basis and is becoming more safe in the hands of qualified men every day. The public has been educated regarding the method in an astoundingly short time by articles in magazines and by the syndicated paragraphs, which every newspaper carries, written by a physician in forceful and convincing style. Nevertheless, the method is not as yet perfected, and the results are not uniformly good. Hemorrhages of serious nature have occurred, and even deaths have been reported. In Barlow's opinion electrocoagulation requires more care, judgment and dexterity than the approved methods of surgery. Salesmen become overzealous in their anxiety to sell apparatus and superlative in their statements as to the simplicity and effectiveness of the method. Some even outline the technique or offer to perform the first applications. Further, sweeping statements in the syndicated medical articles lead the laity to believe that only one or two sittings are necessary and that in 5 days the tonsil has vanished. Only small areas must be coagulated; large sloughs may be followed by severe bleeding. The active electrode must be kept well within the tonsil; if the pillars are invaded a stormy reaction is sure to follow. When the surface of the tonsil is swabbed with cocaine too much may be used or some may be swallowed. In a patient just recovering from tonsillitis the treatment may precipitate quinsy or arthritis. On the whole, the method is admirably adapted to certain cases in the hands of men trained in its uses, but it is far from satisfactory as used by the profession at large without training.

Dissecting Aneurysm of the Aorta.—Six previously recorded cases and 11 new cases with necropsy (4 with roentgenograms of the chest) are reported by WOOD, PENDERGRASS and OSTRUM (*Am. J. Roentgenol.*

and *Rad. Therap.*, 1932, 28, 437). Roentgenologically there is deformity of the supracardiac shadow. Frequently an arcuate excrescence extends outward from some point on the aortic arch. The protuberance may or may not pulsate. The shadow produced by extension of the dissection along one or more of the large branches of the aortic arch is probably the most nearly pathognomonic roentgenologic sign. Displacement of the esophagus and trachea may occur. The heart is usually enlarged. Fluid is frequently present in the left pleural cavity. Non-fatal rupture of the aneurysm into the left pleural cavity occurs quite often in these cases. Nonfatal rupture of the aneurysm into the peri-aortic tissues may produce a bizarre roentgenographic appearance.

NEUROLOGY AND PSYCHIATRY

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Panic.—DIETHELM (*Arch. Neurol. and Psychiat.*, 1932, 28, 1153) states that the more frequent panics can be grouped under "incidental panics." They are merely an incident in the course of a psychosis. They may occur in any setting as a reaction to an unbearable, threatening situation to which the patient is unable to adjust himself. The symptoms of a panic are extreme fear, but one may also notice suspiciousness, projections, misinterpretations, ideas of reference and delusions of persecutions that may or may not be self-depreciatory, according to the setting in which the panic occurs. The behavior is often bewildering because of the many apparently contradictory features, which can be explained by the patient's inability to decide to whom he should turn or where to find his enemies. In the interval between outbursts of panic the patient may be quiet or restless, in good rapport with his environment or on suspicious guard. The high and extremely variable pulse rate is one of the best indications of the still persistent tension which can also be recognized from other sympathicotonic symptoms. Knowledge of the bodily changes in panics is meager, partly due to the lack of coöperation in states of extreme fear and insecurity. The author gives a situational grouping of the panics: (1) Sexual insecurity; difficulties aroused by homosexuality, constitutional instability, masturbation and emission, sex tension and desires, fear of impotency. (2) Financial insecurity. (3) Conscientiousness and inadequacy panics; those incapable of carrying responsibilities, frequently due to a feeling of being inadequate to the requirements of a situation. (4) Philosophic insecurity; this includes the person's reaction to the problems of death and eternity, which frighten certain people because they feel unable to cope with situations that are unintelligible and are

mystical to them. Less vital situations may produce incidental panics; impending operations, fear of recurrence of a panic. An analysis of the situations proves that situational factors are not leading in producing a panic, but that constitutional makeup has to be considered pre-eminently. Panic reactions can be grouped into paranoid and disintegration panics. In the first form the personality remains more or less intact, although deeply involved, as seen by systemization of the delusions, which may last several months. In the disorganization panics a schizophrenia-like picture results. The stupor was caused by fear of action in a state of complete insecurity, or was the expression of great aversion. The study of reaction, situation and individual personality is an approach that leads to a careful treatment of the patient. It requires analysis of the disturbing and helpful minor situations of the 24 hours as well as the major situations that precipitated the illness, and it forces one to attempt to adjust the past and future situations in the patient's life. There should be protection against suicidal attempts, a frank attitude on the part of the physician and of whoever comes in contact with the patient. Every step of the routine must be carefully explained and necessary modifications made. Premature transfer to a better ward or sudden withdrawal of sedatives may precipitate an increase in insecurity or cause a panic outburst. Divided doses of small amounts of barbitol four times a day and hydrotherapy decrease the tension. One is thus able to establish the basis for cooperation and confidence. A discussion of the more fundamental factors must be delayed until the patient feels able to face his shortcomings and can also give due appreciation to his assets. Interviews must be short and end with reassuring formulation. In most cases the patient recovers after a few weeks or months, but the illness may last more than a year and end in a final adjustment. Some panics are only the initial stage of a serious schizophrenic illness. The duration and final adjustment depend much on intelligent treatment.

PATHOLOGY AND BACTERIOLOGY

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Incidence of Gastric Ulcers in Albino Rats Fed Diets Deficient in Vitamin B.—In a controlled series of studies, DALLDORF and KELLOGG (*J. Exp. Med.*, 1932, 56, 391) tabulate and describe ulcerative lesions of gastric mucosa in rats receiving diets deficient in the antineuritic factor of vitamin B. Sixty-four animals were examined. Of these, 44 received diets totally lacking in or with an adequate supply of vitamin B (B). Twenty received diets containing adequate amounts of B. Ulcera-

tions of gastric mucosa were found in 73 per cent of the former, and in not one of the latter. The ulcers were in many cases multiple. Eight were chronic. The lesser gastric curvature was the favored site. None of the ulcers were visible to the naked eye. Even so, the authors state that the size of the lesions in rat and man is comparable, taking the disparity in size of the organs into account. Plates are included with several magnifications of representative ulcers. The concluding statement is that "albino rats deprived of vitamin B commonly develop ulcers of the gastric mucosa."

Nerve Changes in the Region of Chronic Ulcer and Ulcer-carcinoma of the Stomach (Ueber Nervenveränderungen im Bereich des Magengeschwürs resp. Ulkuskarzinoms).—KATSURASHIMA (*Mitt. über allg. Path. u. path. Anat.*, 1932, 7, 285) states that in the region of chronic peptic ulcer as well as carcinomatous ulcer of the stomach the nervous elements show either regressive or progressive changes. In 25 of 53 cases of both conditions the nerves show themselves as very resistant to change, more resistant than the muscle elements. Proliferative changes may show themselves as hypertrophy and mild hyperplasia of the axis cylinders in the denuded nerve bundles on the surface of the ulcer, while 30 per cent of the cases show bulbous outgrowth into the scar tissue of axis cylinders out of the stumps of amputated nerve bundles (so-called amputation neuroma). Perineuritis was seldom observed. Progressive changes of the nervous apparatus were absent in 53 per cent of the cases. In these the nerves were affected by necrosis directly from the ulcer, or they showed other regressive changes. When one compares the primary gastric carcinoma with the ulcer-carcinoma it is striking that in the latter there is a more frequent occurrence of the different kinds of neuroma. The nervous elements in the advanced carcinoma show by and large, passive or regressive changes. In the cancer tissue there were no neuromata found. The individual axis cylinders between cancer cells may be well preserved or show only regressive phenomena. So-called Renaut nodules may occur in gastric nerves. These consist mostly of newly formed, laminated endothelial cells, similar to concentrically laminated Schwann cells.

HYGIENE AND PUBLIC HEALTH

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Studies on Ringworm Funguses With Reference to Public Health Problems.—Attempts by BONAR and DREYER (*Am. J. Pub. Health*, 1932, 22, 909) to grow fungus on sound clean wood have yielded only

negative results. Fungus may grow readily on floor material that is covered by a coating of slime or algal growth. Results of the application of certain disinfectants to growth on slime covered blocks of floor materials are given. The complete killing of *Trichophyton interdigitale* borne in skin scales, by 1 per cent sodium hypochlorite solution requires a time period of 1 hour or longer. Thermal death point studies on spore suspension, cultures grown in fabrics, and on material imbedded in skin scales show complete killing of the fungus in 10 minutes' time at 75° C., or lower in some cases. The efficiency of the fungicidal action of standard power laundry practice is shown to vary with the nature of the fabric handled and with the temperature applied to the different materials. The standard practice for white cotton fabrics shows a good margin of safety, while that employed for woollens and colored fabrics is doubtful. The application of standard "dry cleaning" solvents to these funguses, either growing in fabric or imbedded in skin scales, is shown to have a negligible action in exposures of 1 to 2 hours.

Permanency of the Mild Type of Smallpox.—CHAPIN and SMITH (*J. Prev. Med.*, 1932, 6, 273) state that the mild strain of smallpox has prevailed over vast regions of the United States for over 30 years. It has continued in an enormous number of lines for hundreds of "generations" and still maintains its early characteristics. Cases of this mild strain of smallpox, like those of most contagious diseases, exhibit many minor variations, but without development of a permanent new type. The variations in the disease can scarcely be due to anything else than variations in the pathogen, what biologists call "fluctuating variations." The writer has been unable to find any evidence that the mild strain has ever reverted to the classical type, that is, that the pathogen of the disease has ever undergone a mutation in that direction. It is true that there have been in this country many outbreaks of the severe classical type. Some have occurred ever year. They have been most numerous near the Mexican border, or at seaports. A large number of these outbreaks of the severe strain have been definitely determined to have arisen from importations. Many more, probably, had such an origin. Most American health officers and epidemiologists who have had experience with the two types of smallpox do not think that as yet there has been any reversion of the mild strain to the old classical strain.

Postvaccination Encephalitis With Special Reference to Prevention.—ARMSTRONG (*U. S. Pub. Health Rep.*, 1932, 47, 1553) states that the only practicable means so far suggested for preventing the encephalitis occasionally noted following smallpox vaccination have to do with the vaccination procedure. A suitable vaccination technique is defined as one employing a small superficial insertion, never over $\frac{1}{8}$ inch in greatest diameter and which employs no routine dressing. Infancy is the best time for performing primary vaccinations insofar as the prevention of postvaccination encephalitis is concerned. Evidence is presented which suggests that inoculation with diphtheria toxoid tends to render mice somewhat more resistant to vaccine virus subsequently administered intracerebrally. It is suggested that primary vaccinations, especially after the first year of life, be deferred until contemplated immunization

against diphtheria or other diseases by means of inanimate antigens has been accomplished. It is suggested that the first dose of diphtheria toxoid be given preferably at 6 months of age and the second dose 1 month later; vaccination against smallpox to follow the second inoculation in from 3 to 4 weeks. The same procedure is suggested for older children also. The hope is expressed that a recent preliminary exercise or mobilization of the immunity or defense forces may lead to a more efficient antivaccine-virus response, with the result that the ensuing reaction may tend to simulate primary infant or secondary vaccinations in their comparative mildness and freedom from postvaccination encephalitis. The suggestion is made that possibly the high percentage of poliomyelitis cases recorded among diphtheria-susceptible children in New York in 1916 may be due in part to an increased resistance to poliomyelitis among children immune to diphtheria.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 20, 1933

Experiments on Chemotropism of Leukocytes.—WILLIAM B. WARTMAN and MORTON McCUTCHEON (Laboratory of Pathology, University of Pennsylvania). Experiments were made to determine whether polymorphonuclear leukocytes are attracted by dead leukocytes. Human blood was centrifuged and a small clump of leukocytes (about 300 to 500 micra in diameter) was placed on a slide and allowed to dry. A drop of fresh blood from the same individual was placed on the dead leukocytes and allowed to spread between slide and coverslip. The preparation was examined with the microscope, at 37° C. The dead leukocytes were placed at one end of the microscopic field and the number of leukocytes which moved to the dead ones and made contact with them was counted. Another field, without dead leukocytes, was then studied, and the number of leukocytes was counted that made contact with an imaginary area having the same size as the clump of dead leukocytes. In 10 experiments the number of moving leukocytes that made contact with the dead ones was 10 per hour; the number in control fields was 2 per hour. It is therefore concluded that in these experiments polymorphonuclear leukocytes were attracted by dead cells.

The Estimation of Ethyl Iodid by the Katharometer in Determinations of Cardiac Output in Man.—J. S. DONAL, JR., and C. J. GAMBLE (Laboratory of Pharmacology, University of Pennsylvania). The chemical methods for the determination of ethyl iodid in estimating the cardiac output in human subjects according to the method of Starr and Gamble are time consuming. This has made difficult the accumulation of adequate data on the output of the heart under pathologic conditions.

Therefore a physical method, the katharometer, based on a comparison of the thermal conductivities of gases, has been adapted to the estimation of ethyl iodid. A sample of respired gas is freed of carbon dioxid and water vapor by exposure to ascarite and phosphorus pent-oxid. The thermal conductivity is then compared in the katharometer with that of a portion of the same gas from which the ethyl iodid has been condensed by passage through a tube immersed in liquid air. This comparison of the thermal conductivities of two portions of the same sample makes the instrument independent of the variations in oxygen content to be met with in respiratory samples.

The calibration of the katharometer is simplified by the fact that, in the determination of cardiac output, a knowledge of absolute concentrations of ethyl iodid is not required; only the ratios of the concentrations of the four samples need be determined. For this reason the accuracy of the instrument over the range encountered in a determination of cardiac output is tested by comparing the electrical readings of a series of known dilutions made from a single ethyl iodid air mixture. The average of forty such tests, made in the course of 18 months, indicates a probable error for a single determination of 0.00055 per cent by volume, or 0.75 per cent of the maximum concentration met with in a determination of cardiac output. This is a somewhat greater degree of accuracy than that attained with the chemical method previously employed.

By means of the katharometer, two determinations of cardiac output can be completed in less than an hour. The number of cardiac output estimations which could be performed conveniently by the chemical method in a week, can be made by the katharometer method in a day. The data secured by this method from 100 patients at the University Hospital are now being analyzed.

The Effect of Unilateral Section of the Peroneal Nerve of the Albino Rat on the Number of Myelinated Fibers in the Intact Nerve of the Opposite Side.—K. TAMAKI (The Wistar Institute of Anatomy and Biology, University of Pennsylvania). The effect of the section of a peripheral nerve on one side on the contralateral nerve has been noted by several observers. This study presents a more detailed examination of this effect. The peroneus nerve of the albino rat was that used. It contains about 2000 myelinated fibers. Section of this nerve on one side causes, after 6 weeks, either a loss of myelinated fibers in the contralateral nerve, or a retardation in the formation of new fibers with advancing age.

In 19 cases, section of the peroneus nerve on one side resulted in an average increase in the number of fibers in the contralateral nerve of 0.9 per cent in 6 weeks. In unoperated rats the normal increase of fibers in the intact nerves is 5.9 per cent in the same period.

Section of the peroneus nerve on one side, therefore, causes either a loss of fibers in the contralateral nerve or a retardation in their formation.

The fibers concerned are regarded as the branches of the main fibers forming the nerve, and the effect produced is referred to substances formed in the sectioned nerve, and acting injuriously on the contralateral neurons.

The Nervous Regulation of Intercostal Respiration.—D. W. BRONK and L. K. FERGUSON (Johnson Foundation and the Department of Surgery, University of Pennsylvania). The factors relating to the nervous control of thoracic respiration have been investigated by recording simultaneously the impulses in nerve fibers to the external and internal intercostal muscles of decerebrate cats. In accordance with the general findings of Adrian and Bronk regarding the grading of muscular contractions, it is observed that greater thoracic respiratory activity is a result of an increased frequency of impulses in single nerve fibers, an increased number of motoneurons in action and an increased duration of discharge, as well as the familiar increase in rate of respiration. The nerve fibers to the external intercostal muscles are found to be responsible for inspiratory activity, those to the internal intercostal muscles for expiration, although this relationship is reversed as regards the interchondral part of the musculature.

In addition to the increase in number of active fibers, increased respiratory activity is, then, a result of an increase in the rhythm of impulse discharge from the individual motor nerve cells and an increased rhythm of the bursts in which these impulses are discharged to the muscles. In order to determine the extent to which these rhythms are independent of rhythmic afferent impulses, experiments have been performed on animals in which both vagi were cut, and in which all muscular contraction was abolished by means of curare. Under such conditions the asphyxia produced by stopping the respiration pump induced an increasing frequency of impulses from a single motor nerve cell. The alternate bursts of impulses in the nerves to the external and internal intercostal muscles were maintained, and it was observed that those cells controlling the activity of the internal intercostal muscles did not discharge during the period of activity of the cells controlling the external intercostals. It is therefore to be concluded that the centers for controlling intercostal respiration carry on rhythmic activity when uninfluenced by rhythmic bursts of afferent impulses from the lungs or from the respiratory muscles and, further, that there is a synergic relationship between the activity of these two groups of cells independent of such afferent impulses.

Observations on the Localization in the Brain-stem of Mechanisms Controlling Body Temperature.*—ALLEN D. KELLER (Department of Physiology and Pharmacology, University of Alabama School of Medicine). The work of Isenschmid and Schnitzler¹ in the rabbit, and of Bazett and Penfield² in the cat demonstrated by extirpation experiments the dependence of normal regulation of body temperature upon the hypothalamic region of the brain-stem. It seemed worth while to localize further in a *qualitative* manner the mechanisms concerned, with a view that this procedure would eventually lead to exact anatomic identification.

* This investigation was begun in the Yale Physiological Laboratory.³ It is being continued with the aid of a grant from the Committee on Scientific Research of the American Medical Association.

¹ Isenschmid and Schnitzler: Arch. f. exp. Path. u. Pharm., 1914, 76, 202.

² Bazett and Penfield: Brain, 1922, 14, 569.

³ Keller, A. D.: Proc. Am. Phys. Soc., 1932.

Three experimental approaches have been used: (1) Complete transection at various levels; (2) localization of conducting tracts mediating heat regulating functions as they passed from the *tonic* cephalic central mechanisms caudal through the mid-brain, pons and upper medulla; and (3) direct attack upon the hypothalamic region itself. The following factors were studied carefully in the preparations after operation: (1) Their ability to maintain normal rectal temperatures at usual as well as low environmental temperatures; (2) the presence or absence of shivering, panting and sweating; and (3) the time relation between the ear vessels and rectal temperature in returning to normal after overheating.

Certain necessary criteria for evaluating material have been adhered to: (1) In semi-acute preparations conclusions were drawn only from lesions that did not eliminate the mechanisms studied and, further, it was made certain that these mechanisms were present at the time of termination; (2) conclusions were drawn in regard to deprivation of paralytic symptoms only when these symptoms persisted as the animals became chronic. (A preparation is considered chronic only after sufficient time has elapsed after operation for the disappearance of edema and organization of debris.)

In all cases the block of tissue containing the lesion or lesions has been sectioned serially, and every third or fifth section stained for fiber tracts. This allows for accurate localization of the gross lesions. In chronic material, cell studies are being made to check the presence or absence of cell groups located adjacent to the gross lesion.

RESULTS. Complete Transections. It was necessary to keep mid-brain cats in incubators up to about 3 weeks after operation. Gradually they were able to maintain adequate temperatures in unheated cages; however, when placed in an ice-box (45° to 50° F.), the rectal temperature fell progressively. In no instance has shivering been observed even up to 7 weeks after operation. In two preparations with sections through caudal tip of mammillary bodies ventrally, overheating has elicited typical panting. On removal from the hot box the ear vessels constricted to streaks long before rectal temperature returned to normal.

Only semi-acute pontile preparations have been studied. They have exhibited no attempt at heat regulation. Shivering has never been observed on cooling and the maximum respiration rate on overheating has been 120 per minute.

Several acute and semi-acute medullary preparations have maintained higher rectal temperatures than mid-brain and pontile animals when housed in the same incubators. Typical slight shivering has been noted in the preparations when cooled and also when heated. Hyperthermia has likewise been noted, whereas hyperthermia has never been encountered in pontile or mid-brain preparations. It seems possible that in these cases the mechanisms at the level of the obex may be stimulated by lesion hemorrhages, and so forth, since some medullary preparations react as do pontile preparations.

Hypothalamus. A bilateral transverse section just rostral to the chiasm, complete unilateral involvement of the hypothalamus and bilateral involvement of approximately the ventral third of the hypothalamus has been accomplished in the cat and dog without showing any gross impairment in heat regulating powers.

When the complete hypothalamus was involved—the mammillary bodies may be left intact—without gross injury to thalamic nuclei above, the animals were identical to mid-brain preparations in their inability to maintain normal temperature and to shiver. Rapid respiration and vasodilation were constantly present even in spite of low rectal temperatures. Typical panting was readily elicited by such maneuvers as pinching the tail, massage, or by spontaneous movement or urination by the animal.

Semi-acute and chronic cats and dogs having lesions involving a portion of the dorsal half of the hypothalamic gray matter bilaterally exhibited a permanent impairment of the power to maintain a normal body temperature at low extremes in environmental temperatures. These animals otherwise displayed normal health, exhibited vigorous appetites and were frequently pseudo-affective.

Analysis of the foregoing observations demonstrates the morphological separation—at least in part—of the “heat production” mechanism from that of the “heat loss” mechanism, the former being located in the more dorsal portion of the hypothalamus, the latter in the cephalic mid-brain. The separate existence of two such central mechanisms was postulated by Meyer.¹

Conduction Paths in Mid-brain and Pons. That conducting pathways mediating heat regulating functions pass caudally *both medially and laterally* through the mid-brain and pons, is evidenced by the fact that cats and monkeys (only low pontile lesions have been placed in monkeys) continue to heat regulate after either bilateral section of the medial quarter segments or the lateral quarter segments of the brain-stem at these levels. At the upper level of the mid-brain the tracts seemed to be fairly well concentrated in the medial quarter segments. In the lower mid-brain and pontile levels there is a definite spread to lateral quarter segments.

¹ Quoted by Hasama: *Arch. f. exp. Path. u. Pharm.*, 1929, 146, 126.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1933

ORIGINAL ARTICLES.

THE INFLAMMATORY REACTION IN TUBERCULOSIS.*

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IN approaching this subject on the occasion of the Gross Lecture, it is appropriate to recall the fact that Samuel Gross was the author of the first comprehensive treatise on pathologic anatomy published in this country,† which appeared in 1839, when Gross had just vacated the chair of General Anatomy, Physiology and Pathological Anatomy in the medical department of Cincinnati College.

It seems particularly apposite to our immediate purposes to recall the views of Gross himself on the two subjects of inflammation and tuberculosis. Thereby we may at the same time take pride in the accomplishments of the past century of endeavor in these fields, and be heartened, in the midst of our own serious perplexities, by the partial conquest of the confusion of thought frankly and forcefully depicted by Gross. Influenced by the current French teaching, which reached its extreme expression with Cruveilhier, Gross stated as a logical assumption that "as a general proposition, liable to few exceptions, all organic diseases, whatever be their seat or extent,

* The Samuel Gross Lecture before the Philadelphia Pathological Society, December 8, 1932.

† The earlier "Treatise on Pathological Anatomy," by William Edmonds Horner (Philadelphia, 1829), although treating certain phases of morbid anatomy in detail, did not attempt to cover in systematic fashion existing knowledge in all departments of this subject as did the "Elements of Pathological Anatomy" of Samuel Gross (Boston, 1839).

are the result of inflammatory action." But, he was careful to point out, "of the essence of disease very little, indeed nothing at all," was known. "The proximate cause of morbid action," he added with apparent resignation, "and the immediate cause of life in the healthy state, are as inscrutable to the human mind as the cause of gravitation, of attraction and repulsion. All we can boast of is that we know something of their effects; beyond this it is extremely problematical if we shall ever be able to penetrate. With this, indeed, every philosophical inquirer after truth should be contented, remembering that the secrets of Nature are not easily detected, and that to God alone belongs the knowledge of the intrinsic property of things." Yet this pious renunciation did not suppress the fundamental research instinct of this earnest investigator, for a scant 5 pages later he invites his reader to proceed with him "to investigate the nature of inflammation, its seat and the phenomena which characterize it."

With his comprehensive inclusions under the term "inflammation" it is not surprising that he considered the tubercle an inflammatory product; but this assumption did not lead him to omit proof in his specific discussion of tuberculosis. There was indeed in 1839 much opposed evidence. Drawing analogies from other types of inflammatory reaction, he reached the conclusion "that all tubercular matter, whatever may be its form, site and extent, is, in the first instance, of a liquid nature, and that it becomes solid only by the removal of the serosity which is always poured out simultaneously with it." In other words, he thought of tuberculous tissue as an exudative manifestation.

The problems that beset Gross in 1839 in understanding the nature of the tubercle were never solved, simply because all effort in this field took an entirely new direction a few years later with the development of the cellular pathology. It is perhaps not entirely gratuitous for me to suggest that the direction of our own efforts may also change in the not distant future with the establishment of unexpected new principles which may save us the necessity of ever solving certain of the troublesome and vexing problems to which I shall call attention tonight.

In a revised edition of his book in 1857, at the dawn of the cellular pathology, Gross supplemented his original exposition of the tubercle with a brief consideration of its cellular aspects. He did not yet see in the new knowledge confirmation of his original views on its inflammatory nature, but he had found no reason in the interim to change his opinion.

In Gross's time the definition of an inflammatory reaction was necessarily different from the several that are in vogue today, and in his view the current definitions were inadequate to cover the phenomena of tuberculosis. Particularly was the time-honored descriptive characterization, in terms of redness, heat, pain and

swelling, deficient. As he pointed out, in tuberculosis any or all of these might be lacking. Insisting on a local origin for every inflammation, he thought of the tubercle as a tissue deposit in reaction to some sort of irritant. Obviously the nature of the latter was entirely unsuspected. Doubtless Gross honestly considered it one of those intrinsic properties understandable only by God. The character of the lesion and its effects, rather than its cause, therefore received the greater part of his attention.

Since the time of Gross and his contemporaries there has been an increasing insistence on a beneficial attribute in the phenomenon of inflammation. Even before his time, certainly from the days of John Hunter, if not earlier, inflammation had come to be considered Nature's way, often ineffective and at the best expensive, of handling a body irritant. Most definitions today emphasize this protective aspect. It is doubtful if Gross, however, saw anything but the unfortunately inevitable in the course of tuberculosis, even though considering it an inflammation.

It was indeed a difficult task for later pathologists to uncover beneficial elements in the tubercle. To the early cellular pathologist the deposit of cells in the individual tubercle and the associated tissue destruction must have seemed as devoid of helpful aspects as the infiltration and destruction by a cancer. Even with the discovery of the tubercle bacillus, small consolation came to those seeking the protective element, for the disposition of the infecting agents within the cells, suggesting their multiplication there, seemed to indicate only a defensive mechanism for the parasite, and not for the unhappy host. It was only with the Metchnikovian era and the new concepts of phagocytosis that solid ground was found for advance with the view that exudative and proliferative aspects of tuberculosis were not only inflammatory in character, but also protective. And the most ardent optimist would have to admit that this protective mechanism was often not merely ineffective, but fraught with danger.

There is no doubt that most pathologists today think of the inflammatory reaction in tuberculosis in terms of its cellular aspects. The vascular changes and fluid exudation are looked upon as attendant phenomena and, by those most teleologically inclined, as attendant phenomena designed to bring to the site of the infection an army of fighting cells. And so much interest has developed in the characteristic cells entering into the structure of the tubercle, that discussions of the inflammatory reaction in tuberculosis have an inevitable tendency to resolve into inquiries on the source of the epithelioid cell.

Before succumbing to this trend, I should like to recall certain general principles of the inflammatory reaction in tuberculosis. In the first place—and this might be assumed, even if not known—the inflammatory response varies greatly, quantitatively and quali-

tatively, in different animal species. A special investigation of this variation in relation to resistance was made by Vorwald,¹ who studied the inflammatory response to human type tubercle bacillus infection in the guinea pig, rabbit, monkey, dog, cat, rat and chicken. His figures show no positive correlation between resistance and cellular reaction but, if anything, an inverse relationship. For example, when a comparison was made of the cellular response to tubercle bacilli in the guinea pig and cat, animals of respectively low and high resistance to tuberculous infection, the inflammatory reaction was found to be vastly greater in the former. The lesion characterized at the outset by the greater inflammatory response, proceeded and continued on a much less favorable course. Presumably those opposed to viewing inflammation as a protective mechanism might wish to use this observation in support of their argument. Certainly anyone looking upon the inflammatory response in the two species as protective would be forced to view the minimal response of the cat as much more effective qualitatively than the quantitatively superior response of the guinea pig. Without going into several other possibilities, I should like to say at once that many observers of this phenomenon would be inclined to dissociate resistance and inflammation in this case entirely, and would try to explain the difference in disease progress in the two animals by other and quite different factors favoring or discouraging survival of the infecting agent.

Before leaving this very interesting subject of variable reaction in animals may I call attention to the peculiar character of tuberculosis in the rat. The statement is often made that the rat is highly resistant to tuberculosis. The truth is that rats, at least most white rats, are not highly resistant, but the disease progresses with extreme slowness in their tissues. As a general rule, however, it progresses as relentlessly as a malignant tumor. This progress is in the face of, or some might say with the support of, a steady production of phagocytic cells that engulf the bacilli. Whether the outpouring of such cells is inflammation is perhaps an academic point only. At any rate within these cells the bacilli thrive until the continued multiplication of phagocytic cells surpasses the mechanical tolerance level of vital organs like the lungs, and the animal dies.

The next general principle meriting consideration is the variability of inflammatory response within an animal species. I refer especially to the modified inflammatory capacity conferred by previous tuberculous infection and the resultant so-called hypersensitiveness. Tuberculous infection does not always bring about the hypersensitive state. Certain animals, like the rat, seem to have no heightened inflammatory reactivity after a first infection. In man, cattle, pigs, fowls, guinea pigs and many other animals the capacity to respond to a new similar infection is greatly enhanced by a previous infec-

tion. This increased reactivity is most easily observed in the familiar Koch phenomenon in the skin. But experiment has shown that most other tissues share in the hypersensitive state, although not in equal degree. With this experimental control it seems fair to interpret certain intense reactions in man that occur in reinfections but not in first infections, as allergic phenomena. The list would include tuberculous pneumonia and the exudative responses of serous membranes. It is generally agreed, too, that in the more chronic phenomena of adult type pulmonary tuberculosis, including excavation (often rather superficially disposed of as a Koch phenomenon), hypersensitivity plays an important part.

The altered reactivity of the hypersensitive state seems to be expressed almost solely in increased speed and intensity of inflammatory response. Sometimes a special influx of certain cells, especially eosinophil leukocytes, is seen, giving a qualitative alteration to the picture, but in the main the difference in reaction from that of first infection lies in the wider dilatation of capillaries and much greater outpouring of plasma and wandering cells. We seem on sure ground in interpreting this enhanced reactivity seen in acute tuberculous inflammation in terms of hypersensitivity. It seems reasonable to suppose that the modified reactivity of chronic infection, however, is a more complicated matter. In recent years there has been an increasing tendency to dissociate the phenomena of allergy and immunity, a trend especially furthered by the extensive work of Rich,² and we may well believe that such matters as halted growth of bacilli, and their more rapid destruction, lead to a slow change in anatomic character of tuberculous lesions, even when lessened hypersensitiveness, or none at all, can be detected by the accepted tests for this phenomenon.

More intimately considered, hypersensitiveness involves a multitude of tissue structures. The most important seems to be the vascular endothelium. A small dose of tubercle bacilli in the skin, or in any of several other tissues, in a normal guinea pig causes a barely detectable local hyperemia. The same dose of bacilli in a previously infected and hypersensitive animal causes intense local vasodilation. The normal vasomotor capillary constriction is completely in abeyance, and blood pours into every capillary in the neighborhood. The extraordinary exudation that occurs when tubercle bacilli or certain elements of their substance come into contact with serous membranes, is also probably based in part on change in the vascular endothelium. When a small dose of tubercle bacilli is injected into the peritoneum of a normal guinea pig no appreciable immediate change can be noted. When the same dose is introduced into a tuberculous guinea pig (but one, I should add, with a normal appearing peritoneum), in a few hours the peritoneal coat is suffused with a delicate pink, is slightly swollen, and 10 to 15 cc. of plasma, containing a good many leukocytes, have oozed

into the peritoneal cavity. It is generally believed that the acute tuberculous effusions in man, such as pleuritis, meningitis, etc., are on a similar basis. Naturally in the more chronic manifestations of tuberculous serositis other factors, such as lymphatic blockage, play a part.

Of particular interest is the apparent sensitization of a wide variety of body cells. Among the most sensitive are the primitive germ cells of the testis. Small doses of tubercle bacilli and their products have no effect on these cells in the normal guinea pig. The same dosage causes prompt degeneration of these cells in the tuberculous animal, even though no known method permits us to see any previous difference in the cells concerned. Perhaps, however, I have digressed from the subject, in discussing a phenomenon not inflammatory but degenerative in nature. However, a similar, if not identical phenomenon can be discovered in leukocytes, which by common consent are intimately concerned with inflammation. Holst³ and Stewart, Long and Bradley⁴ have called attention to the toxic effect of tuberculin on leukocytes from tuberculous animals, contrasting it with the innocuousness of this substance for the same cells in normal animals. Rich and Lewis⁵ and Aronson⁶ have shown a similar effect of tuberculin in tissue culture on the wandering cells of the spleen and bone marrow of tuberculous guinea pigs. These results were obtained with tuberculin and not tubercle bacilli, but, as I shall point out later, it is "tuberculin" that is largely responsible for the acute response in tuberculous infection. Apparently the effect of tubercle bacilli and their specific product tuberculin on leukocytes is in accordance with the general pharmacologic law that small doses of injurious substances stimulate, whereas large doses kill. The enormous output of polymorphonuclear leukocytes in tubercle bacillus reinfection and in the tuberculin reaction is a familiar picture, and if the capillaries are examined under these conditions it will be found that they are crowded with leukocytes. Apparently in the tuberculous and hypersensitive animal, tubercle bacilli have a far greater chemotactic effect than in the normal animal, and the total inflammatory response is correspondingly altered. An increased phagocytic action by the leukocytes of the infected animal has long been known (Meakins⁷), and has been shown to be associated with the presence of serum antibodies (McCutcheon, Strumia, Mudd, Mudd and Lucké).⁸

At this point it is perhaps appropriate to attempt an analysis of the inflammatory reaction in tuberculosis in terms of the elements of the bacillus that appear responsible for different phases of the tissue response. It is now well known that most of the anatomic features of experimental tuberculosis can be reproduced by the injection of certain purified substances obtained from the bacillus. The tuberculin reaction is an illustration in point. The acute inflammatory response elicited when tubercle bacilli are introduced into

the tissues of a tuberculous animal seems no different from the reaction obtained if an extract of the bacillus, certain nitrogenous products of its growth or, finally, a pure protein isolated either from the bacillus or the medium of its growth, be substituted for the living microorganism. Minute amounts of this protein, which has been studied exhaustively by Seibert,⁹ call forth an acute reaction in tuberculous guinea pigs, which is grossly and microscopically indistinguishable from that produced by an equivalent amount of tubercle bacilli. Certain derivatives of this protein, which probably occur in quantity in ordinary tuberculin, incite a closely similar response.

A close likeness of the tubercle itself, and of chronic proliferative tuberculosis, can be brought about through the use of another class of substances that can be isolated from tubercle bacilli. A group of highly purified lipoids have been prepared from these microorganisms by Anderson,¹⁰ which have been found by Sabin¹¹ and her coworkers to produce masses of new tissue much like tubercles. Of the several lipoids isolated and purified, a phosphatid has proved the most active in stimulating the formation of tuberculous tissue, and its effect on the production and changing appearance of epithelioid cells is such as to lead Sabin to consider tuberculosis in some respects a "phosphatid disease."

Having discussed some of the more general phases of cellular reaction in tuberculous infection, we may now consider the nature of the cellular response itself. It has been known for many years that the immediate reaction when tubercle bacilli are introduced within the tissues is an outpouring of polymorphonuclear leukocytes, and everyone familiar with the histology of the reaction of reinfection is aware that this cellular exudation is greatly intensified by hypersensitiveness. Relatively little stress has been laid upon this polymorphonuclear response, but it is really of more than passing significance. Vorwald¹² has made a careful study of the early reaction to intravenous injection in the rabbit lung, which emphasizes the localizing effect of the response upon the bacilli introduced. In less than an hour after the injection all the bacilli are within polymorphonuclears, and the latter are aggregated into tight masses which represent the site of subsequent tubercle development. Within a few hours phagocytosis of the bacillus-laden polymorphonuclears by large mononuclears occurs, and is followed by their digestion, so that at 24 hours only traces of the former may remain, with the bacilli lying free in the cytoplasm of the large mononuclears. Thus the determinative effect of the polymorphonuclear response upon the localization of the tubercle is clear. It may be suspected that the polymorphonuclear leukocyte that holds the bacillus for a time may have some effect on the microorganisms, supplementing the later action of the large mononuclear, but nothing definite in this respect is known.

On reinfection, the same phenomenon of initial polymorphonuclear response with prompt localization of the bacilli is observed. The only difference is that the cellular outpouring is faster and on a greater scale. Whether or not destruction of the bacilli is aided in this process, the inflammatory reaction must constitute a significant impediment to spread of the bacilli by way of the body fluids. Krause¹³ and Willis¹⁴ have laid great stress on the localizing effect of the allergic reaction on tubercle bacilli injected into the skin of tuberculous animals and, as I have taken pains to show, the first localization is carried out almost exclusively by the polymorphonuclear cells.

Although relatively little attention has been paid to the polymorphonuclear reaction that I have just discussed, there has been enormous concentration of effort on the source, nature and activity of the large mononuclear cells which, in various stages of transformation, make up the more mature tubercle. The same cells are of course concerned in chronic inflammations in general and, as Opie¹⁵ has recently stated concisely, "The problem of the origin of these cells is nearly half a century old, and whether they come from the blood stream or from the fixed tissues or both is no better understood when their accumulation accompanies the healing of a pyogenic abscess than when as 'epithelioid cells' they form the essential element of the tubercle."

Among the many complicating factors in determining the origin and rôle of the large mononuclear phagocytes in tuberculosis, are the variations in their form and action in different animals used for experimentation and even in different organs of the same animal. Corper and his associates¹⁶ have noted a great variability in the accumulation of particulate matter, including tubercle bacilli, in the fixed phagocytes of different organs, and Lurie¹⁷ has presented evidence of a greater destructive capacity for tubercle bacilli in the mononuclear cells of the liver, splenic pulp and bone marrow than in those of lung, kidney and spleen corpuscle. Among the first significant studies on the source of the epithelioid cell was that of Evans, Bowman and Winternitz,¹⁸ who found by the simultaneous injection of vital dyes and tubercle bacilli that in the liver it was the Kupffer cells from which growing tubercles originated. But even in this case it appeared evident to the authors that in the course of development of epithelioid cells from Kupffer cells, numerous large mononuclears of different source were enmeshed in the growing mass and henceforth took part in the tubercle formation.

In the lung a predominant rôle has been credited to the alveolar phagocyte, but the origin of this cell has long been in continued dispute. At present there seems to be a tendency to agree that it is a mesenchymal fixed tissue cell of the alveolar septa (Gardner and Smith,¹⁹ Fried,²⁰ Lang²¹ and others), but there is evidence that

a good many of the mononuclears in lung tubercles and other pulmonary inflammations come from the blood stream also (Foot²²).

In the peritoneal cavity the situation is at least as complicated. Sabin¹¹ and her coworkers have laid great stress on depots of primitive monocytes in the so-called "milk spots" of the omentum. On injection of tubercle bacilli or tubercle bacillus lipoids into the peritoneal cavity multiplication of these cells occurs, according to their reports, with the production of tubercles. At first a rather sharp distinction was drawn between the long known, large fixed-tissue phagocytes, or clasmatoocytes, and the monocytes, which could be found in a similar form both in tissues and the blood. Gardner,²³ however, in examining the peritoneal reaction to primary and superinfection in the rabbit, was unable to discover any difference other than in physiologic activity between these two cells in the peritoneal exudate. What he did find were masses of cells of this general class adhering to the free surfaces of the cavity a few hours after infection. They appeared to arise from cells of the same sort, of undetermined prior origin, and to give rise to large masses of mononuclear cells through mitotic division.

I have cited but a minute fraction of the literature on this detail of tubercle formation, the origin of the epithelioid cell, but I may simply say, as to the rest, that the mass of evidence presented is almost hopelessly confusing. Many skilled cytologists, not primarily pathologists, have entered into the problem without settling it. It therefore must appear presumptuous for one with no such skill to take part in such a competition. Yet I should like, very briefly, to present some evidence of my own on the subject. I may say in advance that it also is inconclusive. It seemed to some of my associates and myself that the cornea, a nonvascular, extremely simple structure, might be a good place to study the details of tubercle formation. To be sure this was the very first tissue in which a serious study of the problem had been made, but much useful information, enabling better interpretation of results, has accumulated since Baumgarten studied corneal tuberculosis in the same quest 50 years ago. My associate, Holley, and I²⁴ found that no significant proportion of large mononuclear cells appeared at the site of tuberculous infection of the cornea until vessels approached the spot. When the infection was at the limbus vascularization and mononuclear infiltration occurred early; when the lesion was at the center both were much delayed. It seemed unquestionable that the influx of mononuclears, replacing the early invading polymorphonuclears, was a consequence of the new bloodvessels. Examination of the latter seemed to furnish a clue. Almost everyone of them was surrounded by a collar of mononuclear cells, which could be traced in successive stages out to developing epithelioid cells. Much difficulty still remained in determining their original source. They occurred not only around the new capillaries but also in their

walls. Had mitoses been numerous we could easily have concluded that they were fixed-tissue cells of the vascular walls multiplying as do other fixed cells. But very frequently cells of identical sort could be seen in the vessel lumina, and occasionally such cells could be seen migrating into and through the vessel walls. This was evidence that the blood monocyte was the source of the perivascular collar of cells, which in turn gave rise to the cells of the growing tuberculous tissue. Colleagues who examined the sections reminded us of the possibility that the migration was the other way, that the cells in the vessel lumina might be coming in and not going out. I shall not dwell upon this experiment longer, because the need for a different type of study, permitting observation of the transit of living cells, is obvious, but my impression remained that a considerable portion of the mononuclear cells partaking in the reaction passed into the vessel walls from the blood stream, slowly accumulated there, gradually migrated into the perivascular tissue, and subsequently underwent increase in size and change in form and became the large mononuclear and epithelioid cells of the tubercle. The process appeared to be accompanied by a minimum of mitosis; this was perhaps the chief argument against a fixed-tissue origin. In fairness I must admit that amitotic division of adventitial cells could have given rise to the same picture.

This fragmentary account of the inflammatory reaction in tuberculosis should be supplemented with some consideration of the effect of the cells concerned on the viability of the infecting micro-organism. As I have said, many pathologists are accustomed to add to their definition of inflammation some teleologic reference to the effect on the injurious agent. As I mentioned a few moments ago, the rôle of the polymorphonuclear leukocyte, other than in its mechanical capacity, has not been determined. As for the mononuclear phagocyte, it is a curious fact that it has been both insisted and denied categorically that this cell destroys the tubercle bacillus within its cytoplasm. The truth seems to be that under some conditions it is effective in this respect, and in others not. To this statement it might be added that the mononuclears of some animal species exert a destructive action, whereas those of others permit growth. Important evidence on this subject has been secured through the investigations of Lurie,¹⁷ who has traced the rise and fall of the bacillary population of the organs of infected rabbits and guinea pigs by counting the colonies of tubercle bacilli that may be isolated from unit weights of these tissues. Multiplication of bacilli, according to his experience, was accompanied by rapid mitotic multiplication of large mononuclear cells. Subsequent decreases in the bacillary count of any tissue were regularly found associated with transformation of the mononuclears into epithelioid cells. It seemed a sound conclusion that the epithelioid cell was a

large mononuclear that had destroyed and partially digested tubercle bacilli.

This view is in contrast with the earlier conclusion of Sabin that the monocyte and its descendant, the epithelioid cells, do not destroy tubercle bacilli, but rather act as nutrient hosts for them, a conception that appears warranted under some conditions of infection. On the other hand Lurie's view is quite in harmony with Smithburn and Sabin's²⁵ more recent picturization of the epithelioid cell as a cell that has reached its distinctive cytoplasmic state through emulsification of phagocytized tubercle bacillus phosphatid. As they have described it, "The lipid is phagocytized by monocytes, or, if the stimulus be great enough, by the primitive cells which give rise to monocytes. After the lipid has been phagocytized it is subjected to a process of intracellular dispersion into finer and finer droplets. After reaching the stage of the finest droplets, no further detectable change takes place."

In all this discussion I have purposely omitted reference to the lymphocyte in the tubercle. It has seemed to me that a large part of the literature on this subject is of uncertain value through failure to identify the cell concerned. What many have been content to label a simple lymphocyte is considered a primitive monocyte by some, whereas others insist that the monocyte is itself a derivative of a primitive lymphocyte. A direct relation between lymphocytosis and resistance to tuberculosis is generally conceded, but the exact relationship of the lymphocyte to the other cells of the tubercle is so much in dispute as to make present discussion of this point unprofitable.

I have floundered in a difficult subject, but in conclusion I would refer again to the perplexities of Samuel Gross in the field I have been discussing. When the first edition of his "Elements of Pathology" was published in 1839, the difficulties he encountered in defending his view of the tubercle as an inflammatory product and understanding its character were formidable and far from solution. In 1857, in the third edition of this book, he repeated most of what he had written in 1839, but added a drawing, with a few paragraphs, showing cells entering into the structure of the tubercle. He attached them as a supplement to his earlier exposition rather than as a solution of his problems. These, however, were never solved, for in the following year, 1858, appeared Rudolf Virchow's "Cellular Pathology Based on Physiological and Pathological Histology," and the worries of Gross and his contemporaries about a deposit of mysterious coagulable fluid in tissues, and subsequent transformation through a clotting nodule to a cheesy mass, were rapidly forgotten. Similarly the vexing cellular problems that I have indicated tonight may be resolved through the discovery of new principles in the large field of physiology, when the details that trouble us may appear inconsequential.

In the meantime the search for facts that will bring into harmony the various views on the origin of the most characteristic cells of the tubercle is being vigorously pressed, as is the effort to bring about a clear understanding of their function and their relation to growth or destruction of the infecting microorganism. The recent extensive work on the action of various chemical fractions of the tubercle bacillus has thrown much new light on these problems, and the introduction of new methods of studying living cells, supplementary to the use of fixed tissue preparations, has also been highly fruitful. Further progress may be expected in both lines. In any event, however, it is obvious that the inflammatory reaction is only one side of the balance in tuberculosis. The physiologic mechanisms concerned in the growth of the etiologic agent are quite as significant for the course of the disease as the inflammatory mechanism, which appears designed by nature to suppress the infecting element. The one field should be cultivated quite as extensively as the other.

Summary. The acute inflammatory response to tuberculous infection varies greatly in different animal species. Its intensity does not correspond directly with the resistance of the species to the disease. In certain animals of low resistance an intense initial cellular response occurs, and in others with high resistance the initial response is slight. In other comparisons no correlation at all can be observed. Factors other than success or failure of inflammatory suppression play a part in determining the fate of the infecting agent.

Within an animal species the intensity of response to tubercle bacilli may vary widely, the chief modifying factor being the hypersensitiveness conferred by previous infection with this microorganism. Not all susceptible animals develop hypersensitiveness. In the hypersensitive animal the inflammatory reaction to tubercle bacilli develops with greater speed and is of greater intensity. Otherwise the reaction is similar to that of first infection. Many cells are affected in the hypersensitive state, including the vascular endothelium and the various types of leukocytes.

The inflammatory reactions of tuberculosis can be reproduced by the use of pure substances extracted from the body of the tubercle bacillus. Chronic productive inflammation is caused by certain tubercle bacillus lipoids, and acute exudative inflammation, similar to acute tuberculosis in man, is caused in the hypersensitive animal by a tubercle bacillus protein and some of its derivatives.

The first cells responding to injection of tubercle bacilli are the polymorphonuclear leukocytes. They rapidly engulf and localize the bacilli, thereby determining the site of tubercle formation. Within 24 hours the polymorphonuclears are phagocytized and destroyed by large mononuclear cells, which complete the development of the tubercle.

The source of these mononuclear cells is still in dispute. It

appears to vary in different organs. In the liver and lung a high percentage of the mononuclear cells of developing tubercles arise from previous fixed tissue phagocytic cells (Kupffer cells and "alveolar phagocytes"). In the omentum, primitive cells apparently identical with blood monocytes give rise to epithelioid cells. In all of these locations, however, blood mononuclears take some part in tubercle formation.

The part played by the mononuclears of the blood is well shown in the cornea. When this normally avascular organ is infected with tubercle bacilli (rabbit, guinea pig, cat) the site of infection, although rapidly permeated by polymorphonuclears, is not invaded by mononuclears until new bloodvessels approach. The new capillaries are seen to be surrounded by collars of large mononuclear leukocytes. Among these mitotic figures are very rare. Migration figures from the vascular lumina are fairly common, and large mononuclears, in considerable excess over the quantity normally found in the blood, can be seen in small vessels. The mononuclears, which thus appear to come largely from the blood stream, wander away from the vessel walls and by hypertrophy and change in structure, without division, become epithelioid cells.

The distinctive cytoplasmic state of the epithelioid cell appears to be the result of destruction of many tubercle bacilli and progressive emulsification of their lipid.

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DIAGNOSIS OF EARLY TUBERCULOSIS.

THE VALUE OF MONOCYTIC LYMPHOCYTIC INDEX DETERMINED
BY SUPRAVITAL TECHNIQUE BEFORE AND AFTER THE ADMIN-
ISTRATION OF TUBERCULIN.

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It is often difficult to make a certain diagnosis of early pulmonary tuberculosis and clearly to differentiate it from numerous other diseases. Usually the physical examination and laboratory data do not offer much on which to base a diagnosis. It is exceptional that bacilli are found in the sputum in the early stage. A blood count may or may not show a slight anemia with a leukopenia or a normal white cell count or a leukocytosis, and on a fixed smear the differential may show an increase of large mononuclear cells or polymorphonuclear cells or lymphocytes. Any one such blood picture of itself is no great help. Frequently a chest plate shows peribronchial infiltration or increased hilar markings or thickened pleura or a combination of these "indicative but not diagnostic lung signs." It is at this point that there is need of confirmatory diagnostic aids.

In the past few years the diagnostic (and prognostic) importance in tuberculosis of the monocyte-lymphocyte index and the total monocytes determined by supravital technique of Sabin have been stressed by numerous investigators. In 1925 Cunningham, Sabin, Sugiyama and Kindwall,¹ using the supravital technique of Sabin,² studied the white blood cells in 75 rabbits after the majority had been inoculated with bovine tuberculosis cultures and a few with human tuberculosis cultures. They concluded that the effect of the tubercle bacillus on the whole system was a profound one, that it consisted in a marked overproduction of diffusely scattered reticular cells, which are the parent cells of monocytes, as well as the other white cells. The particular effect of the tubercle bacillus on the reticular cell was definitely to force it toward the production of monocytes. They determined that the ratio of monocytes to lymphocytes was of fundamental importance. They found that normally the average ratio was: monocytes, 943; lymphocytes, 2805; index, 2.9. When the reaction to disease was very unfavor-

able the ratio was: monocytes, 3469; lymphocytes, 2799; index, 0.8. When the reaction to disease was favorable the ratio was: monocytes, 854; lymphocytes, 3047; index, 3.6. Thus a marked and continued reversal of the normal ratio, provided the monocytes were increased in actual number, was a consistent indication of the malignant stage in the reaction of the animal to the disease. The reverse was likewise true when the lymphocytes were markedly and consistently higher than the monocytes, even though the actual number of monocytes was somewhat above normal, they found arrested tuberculosis without fail.

In 1928 Cunningham and Tompkins³ studied with the same technique the white blood cells of 71 tuberculous patients. For a normal standard of human blood as a comparison they used the figures of Sabin, Cunningham, Doan and Kindwall.⁴ They likewise concluded that the monocytes in the blood are practically always increased in tuberculosis (and are stimulated in phagocytic activity), that the changes parallel the grade of clinical activity, that lymphocytes in the blood are an index of resistance and parallel increased resistance, and that the relation of monocytes to lymphocytes is a useful mathematical expression for the extent of invasion compared to that of resistance.

In 1929 Blackfan and Diamond,⁵ studying the bloods of 17 infants with the Sabin technique, demonstrated the same principle of monocyte-lymphocyte relationship, and in 1931 Hamil⁶ arrived at similar conclusions after an evaluation in infants and children of monocyte counts by the supravital staining method.

In 1931 Grieger,⁷ working under the direction of Cunningham, performed experiments which indicated that there was no storehouse for monocytes in normal nontuberculous animals capable of supplying large numbers of these cells on acute demand, but that such a storehouse was developed in the tuberculous animal. He injected suspension of colon bacilli into tuberculous and nontuberculous animals. In the nontuberculous animals after injection he obtained a moderate leukocytosis with a marked increase of the neutrophils, a decrease of the lymphocytes and a slight decrease of the monocytes. In the tuberculous animals after injection there was a marked leukocytosis with a marked increase in the monocytes, a moderate increase in the neutrophils and a slight decrease in the lymphocytes.

A practical application of these studies seems apparent, as they might be valuable in the diagnosis of early tuberculosis. Since monocytes are increased in tuberculosis and the monocytic-lymphocytic index is of such importance diagnostically, monocytes should be increased dramatically in tuberculous subjects after focal tuberculin is administered, and monocytes should not be increased after administration to normal nontuberculous patients, as there is no storehouse in the normal which is capable of supplying large numbers of these cells on acute demand (systemic reaction to tuberculin).

TABLE 1.—TABULATED CASE DATA.

Date.	Total W. B. C.	Mono.	Lym.	Index.	O. T.	
4/17 4/21	7,000	140	840	6.0	1 mg. I. D. 1 mg. S. C.	Case 1, male, aged 24 years; hemoptysis in 1930; in tuberculosis ward for 3 mos.; Roentgen ray: peribronchial and vesicular infiltration in upper lobe of right lung and thickening of lower bronchial trees; in midlung zone on right side is evidence of small cavity.
4/22 4/23	13,000 11,000	910 440	1,040 2,860	1.0 6.5	Slight local but no focal reaction. Reaction entirely cleared up; no fever; Roentgen ray: no evidence of focal reaction.
8/14 8/18	8,000	240	1,120	4.6	1 mg. I. D. 1 mg. S. C.	Case 2, male, aged 45 years; chronic cough, loss of 25 pounds; rales in left apex; Roentgen ray: peribronchial and vesicular involvement of both lungs, more extensive on left.
8/20 8/21	9,500 7,000	760 560	1,040 840	1.3 1.5	Local reaction; increase in fever; aggravation of physical signs; Roentgen ray: tracheobronchial adenopathy and thickening of bronchial trees on both sides, more marked on left; there is evidence of vesicular involvement and numerous small cavities in midlung zone on left.
2/11 2/23	8,500	510	1,360	2.4	1 mg. I. D. 1 mg. S. C.	Case 3, male, aged 30 years; hemoptysis, dyspnea, fever, loss of weight; apparent emaciation; harsh breath sounds; no reaction.
2/24	9,000	450	1,530	3.4	Roentgen ray: evidence of vesicular involvement of right apex and infraclavicular region on the left side.
2/26 2/27	9,000	540	1,620	3.0	2 mg. S. C.	No reaction.
2/28	11,000	2,200	1,100	0.5	Definite local and focal reaction; rise in fever, continued reaction (rales heard, right apex).
3/1 3/5 3/6	10,000 11,000 10,000	2,000 2,640 1,600	1,000 1,320 800	0.5 0.5 0.5	Roentgen ray: focal reaction in hilar zone of first and second interspace and in right apex.
8/3 8/15	6,000	60	1,440	26.0	1 mg. I. D. 1 mg. S. C.	Case 4, male, aged 31 years; loss of weight; chronic cough, chest pains; undernourished; physical signs of thickened pleura; Roentgen ray: evidence of adhesions between visceral and diaphragmatic pleura at costophrenic angle on both sides; thickening of interlobar pleura on right side, thickening of apical pleura on both sides; no definite vesicular involvement.
8/16 8/17	5,500 6,000	550 600	990 720	1.8 1.2	Marked local and febrile reaction. Roentgen ray: evidence suggestive of slight focal reaction in hilar and midlung zone of first interspace on right side.
8/14 8/25	7,000	560	980	1.7	1 mg. I. D. 1 mg. S. C.	Case 5, male, aged 26 years; cough, loss of weight, weakness; no definite physical signs; Roentgen ray: considerable increase in lung markings with thickening of lower bronchial tree on right side; no definite vesicular involvement.
8/26 8/27 8/28	9,000 12,000 20,000	1,080 2,160 3,200	1,260 960 1,600	1.1 1.5 0.5	Marked local reaction; marked febrile reaction. Roentgen ray: focal reaction in hilar zone of second interspace.
8/10 9/1	9,000	450	2,250	5.0	1 mg. I. D. 1 mg. S. C.	Case 6, male, aged 30 years; weight, 120 pounds; pain in chest (costochondral) aggravated by working; loss of weight; cough; Roentgen ray: hilar shadows in perihilar zone;
9/2 9/3	8,500 11,000	850 1,100	785 1,320	0.92 1.2	Slight local reaction, febrile reaction. Roentgen ray: no evidence of tuberculin reaction; patient refused treatment, returned to work.
9/15 11/14	Rectal abscess developed; he lost 15 pounds. Roentgen ray: evidence of slight vesicular involvement in right apex which was not seen in previous examination.
9/15 10/1 10/2 10/3 10/4	8,000 9,000 9,000 9,000	320 900 900 900	960 990 990 900	3.0 1.1 1.1 1.0	1 mg. I. D. 1 mg. S. C.	C No local reaction. Roentgen ray: evidence suggestive of slight reaction of lungs in hilar zone of right lung opposite second interspace
3/27 4/5	4,000	200	920	4.6	1 mg. I. D. 1 mg. S. C.	C Slight hemoptysis negative; no fever; no local reaction.
4/9	5,000	250	1,250	5.0	3 mg. S. C.	Chial trees thickened; no vesicular involvement.
4/10	5,000	250	1,000	4.0	No febrile, no local reaction. Marked local reaction; febrile reaction; Roentgen ray: evidence pointing to slight focal reaction in hilar zone of the first interspace on right side of right apex.

TABLE 1.—TABULATED CASE DATA —(Continued.)

Date.	Total W. B. C.	Mono.	Lym.	Index.	O. T.	
3/20	8,000	720	2,320	3.2	½ mg. I. D.	Case 9, female, aged 14 years; anorexia, fever, nervousness; P. P. negative. Roentgen ray: hilar shadows markedly exaggerated. Between upper and middle lobes is thickened, no vesicular involvement.
3/21	85,000	850	2,250	2.6		
3/25	2½ mg. S. C.	
3/26	9,000	360	2,340	6.0	No focal, no local reaction.
3/27	9,500	380	1,900	5.0	Roentgen ray: no focal reaction.
8/20	10,500	420	1,260	3.0	Case 10, male, aged 28 years; headaches, loss of weight; increased expiratory phase over right apex; Roentgen ray: exaggerated hilar shadows; evidence of thickened pleura (left apex); lung markings increased; no evidence of vesicular involvement.
8/25	10,000	800	1,200	1.5		
8/26	1 mg. I. D. 1 mg. S. C.	
8/27	10,000	700	1,200	1.7	Marked local reaction; marked febrile reaction; Roentgen ray: no evidence of focal reaction.
9/19	Case 11, male, aged 30 years; influenza in 1918; chronic cough; Roentgen ray: peribronchial infiltration of apical and first interspace bronchi on left side; the midlung zone of the second interspace on right side shows an area of lung reaction which is suggestive of vesicular involvement.
11/1	7,000	350	1,050	3.3		
11/2	½ mg. I. D. ½ mg. S. C.	
11/3	6,000	360	960	2.9		Slight local reaction; no febrile reaction; Roentgen-ray: no evidence of lung reaction from tuberculin.
11/4	8,000	400	1,200	3.0	
8/27	Case 12, male, aged 15 years; pains in chest; no loss of weight; Roentgen ray: peribronchial infiltration of apical and first interspace bronchi on left side; evidence pointing to slight vesicular involvement in left apex.
9/2	8,000	320	1,440	4.6	½ mg. I. D. ½ mg. S. C.	
9/3	9,000	360	1,640	4.5	
9/4	9,000	540	1,080	2.0	Slight reaction locally. Roentgen ray: no focal reaction; lung fields clear.
4/6	Case 13, female, aged 12 years; weakness, inability to gain weight; Roentgen ray: tracheobronchial adenopathy and considerable peribronchial infiltration in perihilar zone on right side.
4/8	5,000	200	1,750	9.7		
4/13	5,500	220	605	2.7		
4/14	6,500	390	1,560	4.0	1 mg. I. D. 2 mg. S. C.	Fever, 102° to 103° F., which developed within 8 to 10 hours. A very severe local reaction; entire forearm became swollen; neutrophils increased from 61 to 90 per cent. Roentgen ray: EPA view of chest shows no evidence of focal reaction.
4/21	6,000	180	1,620	9.0	
4/22	10,000	100	800	8.0	
8/14	9,000	360	1,080	3.0	½ mg. I. D. 1 mg. S. C.	Case 14, male, aged 22 years; pain in right side of chest; cough; pain aggravated by coughing; Roentgen ray: EPA view of chest shows median lobe abscess. No reaction, either local or focal.
8/15	7,500	450	1,050	2.3		
8/16	5,500	220	770	3.5	
7/17	Case 15, male, aged 13 years; undernourished, pale; indefinite physical signs; Roentgen ray: tracheobronchial adenopathy with peribronchial infiltration and reaction in first interspace left side; no evidence of vesicular involvement.
9/10	9,000	450	1,080	2.4	½ mg. I. D. ½ mg. S. C.	
9/11	8,500	425	1,010	2.3	
9/12	9,000	450	1,170	2.6	No local reaction, no febrile reaction. Roentgen ray: no evidence of focal reaction.

NOTE.—Total W. B. C. = total white blood cells; Mono. = monocytes; Lym. = lymphocytes; O. T. = old tuberculin; I. D. = intradermally; S. C. = subcutaneously.

Wells and Long,⁸ who have reviewed the complex and controversial subject of tuberculin, state that the majority of investigators today consider the tuberculin reaction a specific one for tuberculous animals sensitized by dead tubercle or related bacilli. Practically all observers agree that the substance responsible for tuberculin potency is a protein or a protein disintegration product. True, there are albuminoses and proteins in the filtrate which are not specific and which sometimes produce reactions similar to true general tuberculin reactions, but, as a rule, such febrile reactions resulting from nonspecific foreign protein usually occur within 8 or 10 hours, whereas the true specific tuberculin reaction is accompanied

by fever and a rise in basal metabolism 24 hours after the injection (Frisch⁹).

Roentgenologic changes in the lung are not likely to occur after a false tuberculin reaction, unless the reaction is a violent one, and a latent process is made active because of damage to the entire organism and resulting lowered resistance therefrom. The lung changes, however, would not be evident for some time, whereas there are demonstrable roentgenologic signs at the height of a true focal tuberculin reaction, that is, 24 to 48 hours after tuberculin is administered.

In order to demonstrate the above principles 15 patients were selected from the Charity Hospital Out-patient Clinic. Two of these patients were known to be tuberculous. The other 13 were young adults in whom it would have been almost impossible to confirm or deny a provisional diagnosis of early pulmonary tuberculosis. All were given old tuberculin intradermally and subcutaneously, in dosage ranging from 0.5 to 1 mg. intradermally, and 0.75 to 3 mg. subcutaneously, and the monocyte-lymphocyte index studied before and after at the height of the focal reaction or at the time the reaction was likely to occur.

Patients 1 and 2 were those known to have had tuberculosis. The first patient, aged 45 years, had been ill for over 10 years. After administration of 0.5 mg. old tuberculin intradermally, and 1 mg. old tuberculin subcutaneously, there was a marked increase of the monocytes from 240 to 760 and shift of the index from 4.6 to 1.3. Simultaneously there was an aggravation of the physical signs in the lungs, a rise in fever and a marked local reaction. The other patient had definite evidence of pulmonary tuberculosis for 5 years. After the administration of 0.5 mg. old tuberculin intradermally, 1.5 mg. old tuberculin subcutaneously, there was a marked increase in the monocytes from 140 to 910 and a shift of the index from 6 to 1. Simultaneously there was a slight local, but no focal, reaction to the tuberculin. There was no rise in fever. Previously (1929 to 1930) this patient had failed to react to focal tuberculin, although he was definitely tuberculous.

In 5 cases (Cases 3, 4, 5, 6, 7) a marked increase in monocytes was obtained simultaneously with the provocation of a focal reaction in the lungs. In only 1 (Case 7) of this group was there any doubt that there was a true focal reaction in the lungs. However, subsequent Roentgen studies, together with physical signs, marked loss of weight and the development of a fistula *in ano*, marked him as truly tuberculous. The monocyte response with monocyte-lymphocyte shift proved to be of more diagnostic value than the Roentgen examination, which failed to demonstrate a focal reaction. The focal reaction accompanied by a monocyte increase and an index shift we regarded as a very strong indication of the presence of tuberculosis.

In Case 8 there was no monocyte response after tuberculin and there was a questionable focal reaction in the lungs.

The patients in 7 cases were regarded as nontuberculous. In none of them was there a focal reaction or an appreciable increase in monocytes. Cases 9, 10, 11, 12, 13, 14 and 15 did not develop fever. One patient (Case 13) developed a marked local reaction, leukocytosis with an increase of the neutrophils from 61 to 90 per cent and an actual decrease in the number of monocytes. There was no evidence of definite focal reaction in the lungs and the fever occurred within 8 or 10 hours after injection, so the local swelling of the arm was considered as nonspecific and due probably to a reaction from protein to which she was sensitized.

The degree of monocyte response is not proportional to the amount of tuberculin administered. The following table, in which are listed the 7 positive cases, clearly illustrates this.

Type of pulmonary tuberculosis.	No. of case.	Old tuberculin administered (mg.).	No. of times monocytes were increased.
Minimal B	3	2½	6.0
Moderately advanced (quiescent)	1	2	6.0
Minimal A	7	2	3.0
Chronic moderately advanced B	2	1½	3.5
Minimal A	5	1½	3.4
Minimal B	6	1½	5.4
Minimal A or B	4	1	21.6

Cases 5 and 3 were about equal in the grade of clinical severity. In Case 5 the total number of monocytes was increased 21.6 times following the administration of 1 mg. of tuberculin, whereas in Case 3 the total number of monocytes was increased only 6 times following the administration of 2.5 mg. of tuberculin. Other similar cases (Cases 8, 6, 7) likewise showed no proportional relationship. The patients with moderately advanced pulmonary tuberculosis (Cases 1, 2) were given 2 mg. and 1.5 mg. of tuberculin, respectively. The increase in monocytes was 6 times in the former, 3.5 times in the latter. It seems, therefore, that although significant monocyte increase with shifting monocyte-lymphocyte indices coincides with specific focal tuberculin reactions, it would be fallacious to reason further that the greater the degree of monocytosis the more marked the grade of tuberculosis. Suffice it to say, that when there is a marked calling forth of monocytes from their "storehouses" after the administration of tuberculin, the diagnosis of tuberculosis is very likely.

Subsequent examinations of these patients many months later confirmed our first impressions.

Summary and Conclusion. It has been demonstrated that the monocyte plays an important rôle in tuberculosis. An increase in the number of monocytes of the circulating blood is indicative of

activity. A study by the Sabin technique of the number of monocytes and relative proportion of monocytes to that of lymphocytes, that is, the monocytic-lymphocytic ratio, often proves of invaluable assistance in diagnosis. In active tuberculosis the monocytes are markedly increased, and there is a reversal of the monocytic-lymphocytic index. In arrested tuberculosis there is an increase in the lymphocytes, with the total number of monocytes increased but less in number than the total lymphocytes. It has also been shown that there is a storehouse for monocytes in the tuberculous subject, which does not exist in the normal nontuberculous subject. If the total number of monocytes and the monocytic-lymphocytic ratio is determined before and after the administration of tuberculin subcutaneously, the blood of patients in which a definite focal reaction is obtained will show a marked increase in the number of monocytes and a shift in the monocyte-lymphocyte ratio. This simultaneous provocation of focal reaction and increase in circulating monocytes is strong evidence of the presence of tuberculosis.

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PROGNOSTIC VALUE OF BLOOD CULTURE IN TYPHOID FEVER AT VARIOUS PERIODS OF THE DISEASE.

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THE earlier classics by such authorities as Curschmann,⁴ Dieulafoy,⁵ Grisolet,⁶ Jaccoud,⁷ Laveran and Teissier,⁸ as well as the modern by such well-known authors as Masters,⁹ Anders,¹ Rogers,¹¹

Cecil,³ Rolleston,¹² Osler and McCrae,¹⁰ and Castellani and Chalmers,² have all emphasized the importance of complications in the prognosis of typhoid fever, but no mention has ever been made of the prognostic significance of blood culture taken at different periods in the course of the disease.

It is the purpose of this paper to study this particular problem which ought to be of some practical value in medical practice.

The clinical records of the Philippine General Hospital from the years 1911 to 1931, inclusive, and of the San Lazaro Communicable Disease Hospital from the years 1927 to 1931, inclusive, furnish the materials for this study. During these periods a total of 5373 typhoid cases were admitted in these 2 institutions. Of this number 1962 cases (36.52 per cent) had blood cultures taken only once during the course of the disease; of these only 544 (27.73 per cent) were positive.

It is common practice among physicians to have blood cultures taken on typhoid suspects during the early period of the course of the disease only for purposes of diagnosis. It is, therefore, unusual to have blood cultures taken in unmistakably frank clinical cases of typhoid and more especially in the later stages of the disease. Furthermore, the majority of the typhoid cases among Filipinos were admitted to the hospital after the first week of illness. These conditions are responsible for the relatively few cases in which blood cultures were made.

The results of the above-mentioned study are presented in the following tables based upon the date when the blood culture was reported; but subsequent studies, based upon the date when the blood of the same group of cases was taken for culture, gave practically the same results:

TABLE 1.—TYPHOID FEVER FATALITY AT DIFFERENT PERIODS IN THE COURSE OF THE DISEASE IN CASES WITH POSITIVE AND NEGATIVE BLOOD CULTURE COMPARED.

Week.	Positive blood culture.				Negative blood culture.			
	Recov- ered.	Died.	Total.	Fatality rate, per cent.	Recov- ered.	Died.	Total.	Fatality rate, per cent.
1st	46	11	57	19.29	123	16	139	11.51
2d	168	74	242	30.57	585	85	670	12.69
3d	98	51	149	34.22	336	48	384	12.50
4th	39	22	61	36.06	103	22	125	17.60
5th	13	13	26	50.00	59	8	67	11.94
6th	3	3	6	50.00	12	1	13	7.69
7th and over .	1	2	3	66.66	15	5	20	25.00
Total	368	176	544	32.35	1233	185*	1418	13.05

* Of this number, 104 cases were verified by autopsy.

TABLE 2.—TYPHOID FEVER FATALITY IN VACCINATED AND NONVACCINATED PATIENTS HAVING POSITIVE AND NEGATIVE BLOOD CULTURES AT DIFFERENT PERIODS OF THE DISEASE COMPARED.

Week.	Nonvaccinated.						Vaccinated.					
	Positive blood culture.			Negative blood culture.			Positive blood culture.			Negative blood culture.		
	Recov- ered.	Died.	Total.	Fatality rate, per cent.	Recov- ered.	Died.	Total.	Fatality rate, per cent.	Recov- ered.	Died.	Total.	Fatality rate, per cent.
1st	32	10	42	23.80	95	16	111	14.41	14	1	15	6.66
2d	137	67	204	32.84	472	77	549	14.03	31	7	38	18.42
3d	83	42	125	33.60	281	45	326	13.80	15	9	24	37.50
4th	34	22	56	39.28	83	20	103	19.42	5	0	5	0.00
5th	13	13	26	50.00	52	8	60	13.33	0	0	0	0.00
6th	3	3	6	50.00	10	0	10	00.00	0	0	0	0.00
7th and over .	1	2	3	66.66	13	3	16	18.75	0	0	0	0.00
Total	303	159	462	34.41	1006	169	1175	14.38	65	17	82	20.73
									227	16	243	6.58

Cases with positive blood cultures (Table 1) tend to present a higher fatality rate than those with negative blood cultures. While the fatality rate in cases having negative blood cultures remains almost at the same level at different periods in the course of the disease, the cases with positive blood cultures consistently demonstrate an increasing fatality as the period of the disease progresses.

It is well known that there is an early septicemia in typhoid fever which tends to disappear with the advance in the course of the disease. It is reasonable, therefore, to observe that the longer the typhoid organisms persist in the blood stream, the more unfavorable the consequence is for the patient. Presumably also a heavier infection has taken place in cases with positive blood culture than in those negative cases in the same stage of the disease. The protective mechanism of the body should be able to dispose of the bacilli more readily in the latter group of cases. Therefore, the significant difference of 19.3 ± 3.91 per cent in the total fatality rate between the groups with positive and those with negative blood cultures, respectively, should not be at all surprising.

Grouping the cases into the vaccinated and the nonvaccinated by different stages of the disease, it appears that in the nonvaccinated patients the fatality is much higher in cases with positive blood culture (34.41 per cent) than in those in which the organisms were not found in the circulation (14.38 per cent). It is also noticeable that a consistent rise in fatality at different periods in the course of the disease occurs among those from which the organisms were isolated from the blood stream, as contrasted with an almost uniform fatality curve of the negative blood culture cases. The difference in fatality between these two groups of cases amounts to 20.03 ± 4.51 per cent, the significance of which may not be ignored statistically.

The fatality difference between the total cases with positive and those with negative blood cultures, respectively, among the vaccinated groups is 14.15 ± 29.42 per cent. It is apparent that the data in these groups of cases are too meager to furnish enough material to constitute an adequate sample.

Summary and Conclusion. Of 5373 typhoid cases, only 1962 (36.52 per cent) had a single blood culture taken during the course of the disease for diagnostic purposes only, and of the cases with blood culture, 544 (27.72 per cent) were positive.

On the whole a typhoid case with negative blood culture is likely to present a more favorable outlook than one with organisms in the blood stream, especially after the first week of the disease.

The longer the typhoid bacilli persist in the circulation the more does the termination of the case tend to be fatal.

The writer is grateful to Prof. Luis Guerrero, Head of the Department of Medicine, for his interest in the work; to Profs. Hilario Lara and Walfrido de Leon, of the School of Hygiene and Public Health, for their valuable suggestions; to Drs. G.

Lantin, M. Lahoz and G. Austria for their coöperation; to Dean F. Calderon, Director of the Philippine General Hospital, and Dr. C. Gavino, Director of San Lazaro Communicable Disease Hospital, for allowing the writer to have access to the records of the institutions.

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DOUBLE BACTEREMIA (STREPTOCOCCUS VIRIDANS AND STAPHYLOCOCCUS AUREUS) DIAGNOSED BEFORE DEATH.

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CASES of bacteremia in which blood cultures have been found positive during life for *S. viridans* and *S. aureus* must be extremely rare, judging from the few reports in the literature. Mixed cultures from the heart's blood at autopsy are of course more common. Epstein and Kugel¹ in 1929, reporting the occurrence of but 2 cases of mixed infection with streptococcus and staphylococcus in 52 positive autopsy cultures, attributed these findings to an agonal invasion. In 1916 Warren and Herrick² in a survey of 134 cases of bacteremia included 7 cases of mixed infection, in 1 of which the *S. hemolyticus* and the *S. aureus* were isolated from the blood of a patient suffering with chronic otitis, mastoiditis and appendicitis.

This patient recovered following an appendectomy. The high virulence and rapid growth of *S. aureus* in the blood usually leads to a rapidly fatal outcome. Clawson³ mentions the incidence of a *S. aureus* infection superimposed on an old healed valvular lesion. There is the possibility, as indicated by Thayer,⁴ that the staphylococcus is preëminently a terminal invader. However, he does not clearly define his concept of a terminal invasion. Horder⁵ lists 1 case in which a streptococcus and a staphylococcus produced an endocardial inflammation, but gives no further details. Libman⁶ mentions a case in which a healing streptococcic endocarditis was secondarily invaded by *S. aureus*.

Case Report. The patient, J. K., a well-nourished female, aged 13 years, became ill on June 18, 1932, 3 days before being admitted to the Jewish Hospital. She complained of general malaise and arthralgia, and excruciating pain in the third toe of her right foot. The next day she had a severe chill followed by a sharp rise in temperature. Many petechial spots soon appeared on the abdomen, thighs, legs and arms, quickly increasing in size and prominence, many coalescing and forming large purplish blotches.

Her *past history* was significant. She had an attack of rheumatism at 5 years of age, all of her large joints being involved. Her tonsils were removed at 6; the appendix at 10 years of age. At 11 a second attack of rheumatism occurred, the duration of which was not recalled. The history was otherwise negative.

Physical Examination (June 21). The patient, a well-developed girl, was apparently very toxic. Her temperature was 105.4° F., and the pulse and respiratory rates were 120 and 22 respectively. The left border of her heart reached the anterior axillary line. A systolic mitral murmur was heard at the apex and a diastolic murmur at the third left interspace parasternally. Lungs and abdomen were essentially negative, the spleen and kidneys were not palpated. The patient's body surface presented multiple scratch marks and petechiæ. The right middle toe and the distal phalanx of the left little finger appeared gangrenous. There were no abnormal neurologic signs.

Progress. For a period of 7 days following admission her temperature remained elevated (between 102° and 105° F.) in spite of the administration of large doses of salicylates. Repeated showers of petechiæ were observed on the skin of the body and on the conjunctivæ. Epistaxis occurred once. Many hyaline and granular casts were constantly present in the urine. Meningism was observed 4 days before death. The spinal fluid examination was negative. Five days after admission harsh breath sounds and impairment of the percussion note were detected over the base of the left lung suggesting the onset of pneumonia. Two days before death she displayed a marked edema of the lower extremities. Death occurred on the 11th day of the disease and the 8th day of her stay in the hospital.

Laboratory Findings: June 21, 1932. Blood: Red blood cells, 3,450,000; hemoglobin, 63 per cent; white blood cells, 9000, with 70 per cent neutrophils. Platelets, 135,000. Blood sugar, 150 mg.; chlorids, 600; urea, 20. Urine: specific gravity, 1012. Many hyaline and granular casts.

The Widal reaction on 2 examinations was negative for typhoid and paratyphoid A and B. Agglutination for bacillus abortus, negative.

On June 22, an Roentgen ray examination of the chest showed the cardiothoracic ratio (transverse diameter of heart-chest) to be 14.3/25 cm. (57 per cent). The lungs were negative except for an intensification of the

root shadows and a dense haziness at the extreme base on the left side. The electrocardiogram was essentially negative.

Blood cultures on June 27 and 28 were positive for the *S. aureus*. A second culture on June 28 was positive for *S. aureus* and also for *S. viridans*. On June 28 a blood culture which had been taken on June 26 was reported as positive for *S. aureus* and *S. viridans*. Approximately 185 colonies of the former and 25 colonies of the latter organism were reported as present in each cubic centimeter of blood.

Autopsy (Dr. B. A. Gouley) revealed numerous fine petechiæ over her entire body. The panniculus adiposus showed occasional petechiæ.

The heart weighed 360 gm. The epicardium was smooth. There was hypertrophy and dilatation of the left ventricle due to a long established chronic aortic valvulitis (rheumatic). The anterior leaflet of the mitral valve contained a friable vegetation the size of a ten-cent piece which had ulcerated mostly on the auricular side. Both coronary arteries were plugged along their middle course by brownish-gray emboli similar in character to the vegetation on the mitral valve. The absence of inflammatory reaction here pointed to the probable immediate cause of death.

Smears from the heart valves taken at autopsy showed such a predominance of staphylococci that it was extremely difficult to detect the few streptococci that were present.

Lungs. The diffuse mottling of congestion was observed with emphysema of the upper lobes, but no actual consolidation was noted. *Intestines* showed numerous petechiæ beneath the serosal surface. *Spleen, liver and kidneys* revealed many recent septic infarctions.

Pathologic Diagnosis. Double bacteremia. Widespread petechial and purpuric rash. Cardiac hypertrophy and dilatation. Rheumatic aortic valvulitis with regurgitation. Malignant (ulcerative) endocarditis of the mitral valve. Lungs: Congestion; mild emphysema. Adrenals: Lipoid exhaustion. Spleen: Congestion, hyperplasia, septic infarction. Kidneys: Septic infarction, congestion. Liver: Septic infarction, congestion. G. I. Tract: Petechiæ.

Conclusions. 1. Mixed bacteremias with the presence of *S. viridans* and *S. aureus* are rare and, when they do occur, tend to be fulminating in character.

2. Such mixed infections are particularly difficult to diagnose from blood cultures because of the multiplication of the staphylococcus in the blood stream to such a rapid degree that the sparse growth of *S. viridans* on culture media is recognized with difficulty.

3. In patients suffering with a proven *S. viridans* infection of the blood stream when the disease displays fulminating characteristics, bacteriologic search should be assiduously made for the presence of a mixed staphylococcus infection.

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A NOTE ON THE EFFECT OF CHLORINATED SWIMMING-POOL WATER ON FUNGI OF TOE RINGWORM.

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RINGWORM of the toes (athlete's foot, dermatophytosis, etc.) has become a hygienic problem in all phases of gymnasium activity. The frequency among students has been adequately demonstrated by Hulsey and Jordan,¹ Legge, Bonar and Templeton² and others.

Definite prophylactic procedures have been recommended by Gould,³ who advocated 10 to 15 per cent sodium thiosulphate foot baths, and by Osborne and Hitchcock,⁴ who favored sodium hypochlorite. The latter workers indicated that a concentration of 0.1 per cent applied for a period of 1 minute was necessary in the test tube to kill fungi (*Trichophyton interdigitale*) representative of the disease in question.

Author's Tests on Fungus in Vitro. Numerous scrapings from a patient who yielded large quantities of fungus on microscopic examination were selected for the tests and their viability proved in cultures. Portions of the scrapings were soaked in water from the swimming pool and kept at warm room temperature. The pool water for this experiment was collected just before noon on Wednesday, January 27, 1932. On this day at 1 P.M. the chlorin concentration was 0.4 part per million at 76° F. Twenty-four girls had used the pool prior to the collection of the sample.

At 30-minute intervals numerous particles were removed from the solution and cultured. They remained positive after exposures to the chlorinated water of $\frac{1}{2}$ hour, 1 hour and $1\frac{1}{2}$ hours. There was not any growth either after 2 hours' or after 17 hours' exposure.

As recently reported by Templeton *et al.*,⁵ this method, employing fungus in tissue as against fungus in culture material, is more representative of natural conditions. As far as can be deduced from this very limited observation on 1 patient,* the chlorinated water of our swimming pool was a fairly efficient fungicide for infectious material which might become detached from the feet of swimmers.

Conditions between the toes are not parallel with those in the test tube or in the swimming pool, being complicated by (1) the accessibility of the disinfectant to the interdigital spaces, and (2) depth of fungus in the skin. Accordingly, 6 women students

* The particular fungus species concerned in this test subject, *Trichophyton interdigitale*, was the one almost invariably encountered in the students at this university (73 out of 75 cultures).

attending swimming-pool classes during January and February, 1932, at this university were selected from 254 who had been examined and classified in respect to the presence of toe ringworm. The details of this classification will be found in another place (Gilman, Spring and Rea⁶). For the purposes of this note, it is sufficient to state that the 6 selected were from 15 instances of infection from which pathogenic strains of toe ringworm species had been obtained.

In testing the effect of chlorination, scrapings were obtained from the toes of the 6 students immediately before the regular 30-minute swimming period and again at its conclusion. The accompanying table indicates the results, namely, that the chlorinated water was not adequate to kill the fungus between the toes. It might be added that an interval of up to 16 hours sometimes elapsed between

OCCURRENCE OF FUNGUS BETWEEN TOES AT SWIMMING PERIOD.*

Student No.	Before.		After.	
	Microscopic examination.	Cultures.	Microscopic examination.	Cultures.
1	+	+	+	+
2	++++	+	++++	+
3	++	+	++	+
4	++++	+	++++	+
5	++++	+	+	+
6	+	-	+	+

* Fungus had been demonstrated by culture from the toes of all of these women on a previous occasion.

collection of materials and culture, thus giving additional time for the chemical to act. Furthermore, all of these women had been in regular attendance at the swimming pool for a several weeks' interval between the first identification of the fungus and the final set of tests. This gave yet further opportunity for the chlorinated water to exert fungicidal effects between the toes, had it possessed any.

Summary. Ringworm of the toes is such a problem among students and gymnasium habitués in general that a possible fungicidal rôle of chlorinated water in swimming pools merits testing. With 6 women swimmers as test objects, it appeared that:

1. It is possible for detached particles of ringworm tissue to retain viable fungi in chlorinated swimming-pool water for $1\frac{1}{2}$ hours. The fungi, however, may be destroyed in 2 hours.

2. Chlorinated water in swimming pools does not effectually reach and kill fungus between the toes during an average 30-minute swimming period.

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DENTAL INFECTION AND SYSTEMIC DISEASE.*

A REVIEW OF THE LITERATURE AND A STUDY OF 883 COLLEGE STUDENTS, INCLUDING COMPLETE DENTAL ROENTGEN-RAY EXAMINATION.

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DENTAL infection is older than the human race. In animals evidences of caries and of pyorrhea alveolaris have been found in the fossilized remains of primitive vertebrates of the Paleozoic era.¹ In both ancient and prehistoric human remains, evidences of alveolar abscesses and other dental infections have been found,² these being associated in some instances with arthritis deformans, and in others with spondylitis and osteitis.³ The first written notice of oral infection as a cause of systemic disease is said to occur in the writings of Hippocrates,¹ and occasional references to the simultaneous occurrence of oral and systemic disease are to be found in the works of many ancient and medieval writers.

In 1809 Benjamin Rush⁴ wrote, "I cannot help thinking that our success in the treatment of all chronic diseases would be very much promoted by directing our inquiries into the state of the teeth in sick people, and by advising their extraction in every case in which they are decayed. It is not necessary that they should be attended with pain in order to produce disease . . ." In 1889 and 1891 Miller^{5,6} published his articles on oral infection, the term "focus of infection" being used in the title of his American contribution. In 1901 Hunter's⁷ book on pernicious anemia expounded the view that this disease is due to infection of the stomach, which, in turn, is generally due to oral sepsis "arising in connection

* Published simultaneously in the *AMERICAN JOURNAL OF THE MEDICAL SCIENCES* and *Dental Cosmos*, which reproduces illustrations omitted here.

with long continued and neglected cario-necrotic conditions of the teeth." Many modern workers including Moorehead,⁸ Irons,⁹ Hartzell¹⁰ and Pemberton¹¹ have added their observations to show the concurrent existence of dental and systemic disease.

In 1911 Goadby¹² succeeded in producing a "condition indistinguishable from arthritis deformans" by the inoculation of cultures from infected teeth directly into the joints of 18 rabbits. Rosenow¹³ has reported the occurrence in experimental animals of gastric ulcer, nephritis, nephrolithiasis, epidemic hiccup and other conditions following the intravenous injection of cultures from infected teeth, and he has also reported the production of these diseases in dogs by amputating the crowns of the teeth, exposing the dental pulp chambers and inoculating the latter with organisms cultured from human foci of infection or from the distant lesions which are presumed to have been caused by these foci. Other reports have been published corroborating Rosenow's work, but there are many authorities who maintain a skeptical attitude toward these researches.

Evidence of another kind, rather unconvincing in character, has had considerable influence in furthering the theory that dental infection may cause rheumatism and arthritis. It consists in the demonstration of nonhemolytic streptococci in the dental lesions of patients suffering from rheumatism or arthritis. It may be regarded as established, however, that nonhemolytic streptococci are to be found in the saliva and about the teeth of normal persons throughout life: that they may usually be cultivated from the roots or the pulps of devitalized teeth, and occasionally from those sites in vital and apparently healthy teeth: finally, that the so-called blind abscess, or chronic rarefying osteitis with granulation tissue, usually yields cultures of nonhemolytic streptococci, though many are found to be sterile. The nonhemolytic streptococcus may be said, therefore, to be a common inhabitant of the human mouth, both in health and in disease. The demonstration of an organism of this group in the dental lesions of patients suffering from arthritis should, therefore, not be given too great emphasis.

Nonhemolytic streptococci have also been reported by Cecil, Nicholls and Stainsby¹⁴ in the blood of arthritic patients with significantly greater frequency than in a control group. Since, however, other workers^{15,16} have been unable to corroborate these findings, it will probably be best for the present to maintain an open mind as to the streptococcic etiology of arthritis deformans.

That disappointing results frequently follow the removal of foci of infection was observed by Billings,¹⁷ one of the earliest and most enthusiastic adherents to the focal infection theory. To explain these failures, he advanced the hypothesis of the implantation of organisms into the synovial tissues themselves, which then became secondary foci of infection. However plausible this theory may be,

it lacks proof. Moreover, numerous writers^{1,11,18,19} have reported the occurrence of rheumatism and arthritis in the absence of any of the ordinarily recognized foci of infection.

Pemberton,²⁰ in his study of 400 arthritic soldiers, writes: "184 patients, or 46 per cent, recovered in the presence of demonstrable surgical foci. This is nearly 3 times the number which improved (65 cases, or 16.25 per cent) after the removal of foci." Mutch,¹⁸ Miller,¹⁹ Badanes,¹ and Broderick²¹ also minimize the importance of dental infection in arthritis, and it is, indeed, common knowledge that many cases of arthritis recover in the presence of demonstrable infection in the teeth and elsewhere, whereas many fail to recover after the most thorough removal of all possible foci.

Another aspect of the focal infection theory which has impressed some writers has been the statistical evidence of the coincident occurrence of abscessed teeth and chronic disease, especially arthritis. The revelation by Roentgen ray of dental infections previously unsuspected has greatly stimulated interest in this subject. Thus Moorehead,⁸ Irons⁹ and Pemberton and Robertson²² found periapical dental infection in 89, 76, and 33.5 per cent respectively of their arthritis cases. The mere demonstration of the frequent association of dental infection and arthritis does not, of course, indicate a causal relationship between the two conditions. Not only is it conceivable that the dental sockets, being actually joints, might themselves present rheumatic or arthritic manifestations,²³ but it is also possible that certain conditions might exist which would exert an adverse effect upon both the joints and the teeth. The most obvious factor of this nature is that of age. Moorehead,⁸ Duke²⁴ and others have shown that with advancing age there is a marked increase in the incidence of dental infection. Black²⁵ believes that almost 100 per cent of persons over 50 years of age have such infection present. It is not surprising, therefore, to find a higher incidence of dental infection in arthritis, a disease of later life, than in diseases to which the young are most susceptible. It should not be forgotten, moreover, that dental infection is very prevalent in patients with diverse diseases: thus Thoma,² Duke,²⁴ Moorehead,⁸ Haden,²⁶ Pemberton,²⁷ and Irons,⁹ report its presence respectively in 88, 81, 74, 68, 58, and 44 per cent of medical cases of various sorts. Its presence in arthritis is found by Moorehead, Irons and Pemberton respectively to be 89, 76 and 33.5 per cent, which therefore is within the range of its reported incidence in unselected medical patients. One may conclude, therefore, that although dental infection is common in arthritis it is by no means limited to this or to any other chronic disease, and that the coincident existence of arthritis and dental infection does not offer any proof of a causal relationship between the two.

Appleton,²⁸ reviewing the records of drafted men during the World War, showed by the use of semi-logarithmic graphs that

recruits exhibiting dental disease did not show an undue incidence of arthritis, appendicitis, gastric ulcer, endocarditis, osteitis deformans, myositis or muscular rheumatism. A weakness in this method of approach, as pointed out by the author, lies in the variable diagnostic criteria used by the different examiners. Moreover, an ordinary clinical examination of the teeth could not be expected to reveal all or even most of the dental infection present. To secure the best possible data, a complete dental Roentgen ray, as well as a careful clinical, dental and medical examination would be required. A dental examination of this kind correlated with a physical examination on a sufficiently large number of individuals to be of statistical value does not appear to have been recorded in the literature up to the present. Black²⁵ made complete dental Roentgen rays on 175 dental students and 225 dental patients, accompanied by a questionnaire into the health of the 400 subjects; but the health findings are not correlated with the dental findings. Hyatt,²⁹ of the Metropolitan Life Insurance Company, made radiograms of 2787 bridged and devitalized teeth, and reported a high incidence of root lesions; but these results were also not correlated with any medical findings. We believe, therefore, that the present study on 883 students is the first of its kind to appear in the literature.

Medical and Dental Study.* The material upon which this study is based consists of 883 students of Drexel Institute, a small college located in the center of Philadelphia. As regards economic and social status, the group represents a well-to-do but not a wealthy class, many students having to work their way through college. Of the 883 students studied, 502 (56.9 per cent) were males and 381 (43.1 per cent) were females. The average age was 18.75 years, the modal age was 18 years, and the great majority fell between the ages of 16 and 21 years (Table 1).

TABLE 1.—SEX AND AGE OF SUBJECTS.

Age.	Women.	Men.	Total.
16	9	12	21
17	76	83	159
18	158	153	311
19	67	100	167
20	26	73	99
21	6	29	35
22	6	27	33
23	3	14	17
24	1	5	6
25	0	2	2
Over 25	5	4	9
Age not stated	24	0	24
Total	381	502	883

* A brief résumé of the dental findings including Tables 2, 3, 4, 5 and 8 appeared in the Proceedings of the Twelfth Annual Meeting of the American Student Health Association, December, 1931, p. 90.

The physical admission requirements are essentially the same as those of other American colleges. Students are excluded because of physical disabilities only when the latter are serious enough to be incompatible with the fulfillment of academic duties, or when they are a menace to health. No cases of arthritis deformans have been recognized among the students during the period of this study (1929 to 1931, inclusive); but, of course, it is impossible to ascertain whether any prospective students were prevented from becoming candidates for admission because of this, or any other disease. In this respect, all that can be said of this group is that it is a representative sample of students, drawn from a typical American city and its surrounding territory. Completeness of records furnished the only criterion for inclusion or exclusion in this study. Most of the students were freshmen, though a few belonged to the upper classes or were graduate students.

The method of study consisted in taking a medical history and physical examination, including a urinalysis. The dental examination was by a competent dental student or by a graduate dentist, and a Roentgen ray film was made of every tooth and edentulous space (10 films for each case). All dental films were read by the same dental roentgenologist (L. M. E.).

The findings of greatest importance, both from the standpoint of frequency and of oral hygiene, are those relating to dental caries. A tooth containing an area of decay, a leaky filling or an unfilled cavity is regarded in this study as carious. Neglected caries is responsible for most of the teeth prematurely lost by the human race. This fact alone makes caries the most important of all dental conditions.

Caries was found with surprising frequency in our study (Tables 2 and 3). Many carious teeth which had not been detected by clinical examination were revealed by the Roentgen ray; and the reverse was also frequently true. This was demonstrated by the fact that 1662 teeth were found carious by clinical examination and 1372 by Roentgen ray; but of these there was agreement only in the case of 237 teeth. In other words 1425 teeth found carious clinically failed to show caries by Roentgen ray, while in 1135 teeth the reverse was true. Therefore, had the teeth been examined without the aid of the Roentgen ray, 1135 carious teeth (40.6 per cent of the entire number) would not have been detected.

TABLE 2.—THE FREQUENCY OF DENTAL CARIES AS DETERMINED BY COMBINING CLINICAL AND ROENTGEN RAY FINDINGS.

Number of students examined	883
Number of students showing caries	733
Per cent of students showing caries	83
Approximate number of teeth examined	27,398
Number of teeth with caries	2,797
Per cent of teeth showing caries	10.3
Average number of carious teeth per student	3.2

Here and in the tables which follow, regardless of the number of cavities in the tooth, it was counted as but one carious tooth. Sound filled teeth are not included.

TABLE 3.—THE OCCURRENCE OF DENTAL CARIES PER STUDENT AS DETERMINED BY COMBINING CLINICAL AND ROENTGEN RAY FINDINGS.

	No. of students.	Per cent.
No carious teeth	150	17.0
Caries in 1 tooth	131	14.9
Caries in 2 teeth	157	17.9
Caries in 3 teeth	121	13.7
Caries in 4 teeth	98	11.1
Caries in 5 teeth	71	8.0
Caries in 6 teeth	48	5.4
Caries in 7 teeth	39	4.4
Caries in 8 teeth	25	2.8
Caries in 9 teeth	11	1.2
Caries in 10 teeth	2	0.2
Caries in 11 teeth	13	1.5
Caries in 12 teeth	9	1.1
Caries in 13 teeth	4	0.4
Caries in 14 teeth	2	0.2
Caries in 15 teeth	1	0.1
Caries in 16 teeth	1	0.1
Total number of students	883	

Theoretically, a tooth with caries which involves either the dentin or the pulp, may act as a focus of infection. Bacteria may be cultured even from unexposed areas of dental caries. The dental artery and vein enter the tooth through its apical foramen and send their branches throughout the pulp. The dentin communicates with the pulp by numerous minute canals, so that micro-organisms, or their toxic products, could conceivably find their way from the dentin to the pulp and thence into the systemic circulation, leading to disturbances in distant parts of the body. If such were frequently the case we should expect in this group of students to find a high incidence of those diseases which are due to focal infection. Actually, however, no cases of arthritis were encountered, and the incidence of rheumatism, heart trouble or chorea was not significantly higher in the students with demonstrable caries than in those without. Of the group whose histories stated that they had had rheumatism or chorea since early childhood, or whose cardiac examination revealed evidences of valvular heart disease, 85 per cent had carious teeth, the average number of carious teeth per student being 3.3. In the group with a negative history of rheumatism or chorea and without valvular heart disease, 82.6 per cent had carious teeth, the average number of such teeth per student being 3.2. These differences are too small to be regarded as significant, and it may be said that the data offer little support for the assumption that caries is a frequent cause for these 3 diseases.

The findings of greatest importance as regards focal infection relate to the incidence of dental granulomata. Granuloma is the synonym for chronic rarefying osteitis with granulation tissue, the so-called but misnamed chronic root abscess of medical parlance. Granuloma was found in 19.8 per cent of the students examined

(Table 4). This lesion is regarded by the majority of physicians and dentists as potentially a dangerous focus of infection. It can be detected only by means of the Roentgen ray though it can sometimes be surmised to be present by clinical examination. A question of considerable importance is whether it is possible to predict from the appearance of a tooth that its root will be found to be the seat of chronic rarefying osteitis with granulation tissue. Obviously, if such a condition can be predicted from a clinical examination, then a complete Roentgen ray examination is of less importance. Table 5 throws considerable light upon the relation of such clinical predictions to facts as revealed by the Roentgen ray. Of 232 proved granulomata, 106 (45.2 per cent) were suspected from the clinical appearance of the teeth. In other words, if only the suspicious teeth had been Roentgen rayed, 126 or over a half of the granulomata would have been missed. On the other hand, 495 teeth presented a suspicious appearance clinically, but were exonerated by the Roentgen ray: thus out of every 6 predictions of granuloma, approximately 1 proved to be correct. Often clinically innocent looking teeth showed granuloma by Roentgen ray, and often dangerous looking teeth presented a normal Roentgen ray appearance at the roots, so that the conclusion seems justified that a dental examination is not complete without a full mouth Roentgen ray. Even the edentulous spaces should be Roentgen rayed, as had been emphasized by Eusterman.³⁰

TABLE 4.—THE FREQUENCY OF GRANULOMA AS DETERMINED BY ROENTGEN RAY.

Number of students examined	883
Students showing granuloma	175
Per cent of students showing granuloma	19.8
Approximate number of teeth examined	27,398
Number of teeth showing granuloma	232
Per cent of teeth showing granuloma	0.8

Here, and in the tables which follow, the term granuloma is synonymous with chronic rarefying osteitis with granulation tissue, the so-called chronic root abscess or blind abscess of medical parlance.

TABLE 5.—GRANULOMA. COMPARISON OF CLINICAL AND ROENTGEN RAY FINDINGS, SHOWING THE RESULTS OF ATTEMPTING TO PREDICT THE PRESENCE OF GRANULOMA FROM THE CLINICAL APPEARANCE OF TEETH.

	Students.	Teeth.
1. Granuloma suspected clinically; found by Roentgen ray	91	106
2. Granuloma not suspected clinically; found by Roentgen ray	100	126
3. Total number of granulomata (1 plus 2)	232	
4. Granuloma suspected clinically; not found by Roentgen ray	333	495
5. Per cent of proved granulomata suspected clinically	45.2	
6. Per cent of suspected teeth showing granulomata	17.6	

The records of the students exhibiting dental granulomata were compared with those without granulomata, to determine the correlation of granuloma with certain physical conditions suspected of being related to focal infection. First the students whose history

cards indicated that they had had rheumatism or chorea since early childhood, or who on examination were found to have evidences of valvular heart disease, were grouped together (Table 6). It was found that the incidence of the above named diseases was actually slightly lower in the students with dental granulomata than in the students without granulomata. This finding does not substantiate the view that granulomata played a significant part in the production of the chorea, rheumatism and valvular heart disease in this group. Nevertheless, one might still hold this view and explain the lack of correlation of rheumatism, chorea, and valvular heart disease with dental granulomata, on the assumption that in the case of the students with the above named diseases, the teeth had been Roentgen rayed at some prior time, and all those with granulomata removed. If such were the case, a higher incidence of missing teeth might be expected in this group than in the students without rheumatism, chorea or valvular heart disease. Such was not found to be the case. There were actually 1.11 missing teeth per student in the entire group studied, and 0.96 missing teeth per student in the 26 persons comprising the chorea, cardiac and rheumatic group.

TABLE 6.—THE ASSOCIATION OF CERTAIN PHYSICAL ABNORMALITIES WITH DENTAL GRANULOMA IN 883 STUDENTS.

	With dental granuloma.		Without dental granuloma.	
	Number.	Per cent.	Number.	Per cent.
Students	175		708	
Rheumatism, chorea, or heart trouble	5	2.9	21	3.0
Underweight (10 pounds or more below standard for height and age)	44	25.1	153	21.6
Albuminuria (albumin, from a trace to a cloud, with or without casts, found in 1 specimen of urine)	12	6.9	27	3.8

Next the records of the students who were found to be 10 pounds or more underweight for their age and height were considered. The incidence of leanness (10 pounds or more underweight) was 3.5 per cent greater in the students with granulomata than in those without (Table 6). Whether this difference is sufficiently large to be significant, can best be determined by employing statistical methods. It has become a convention to regard twice the standard deviation of simple sampling³¹ as the minimum significant difference.* The observed 3.5 per cent is found to be 0.97 of its standard deviation;† and therefore, according to these criteria, too small to be significant. To state the matter a little differently: it has become conventional to regard a variation as not significant if there is a greater than 5 per cent probability of its occurrence being

* Three times the standard deviation is also used.³²

† The formula employed was that of Yule,³² namely:
$$\epsilon \frac{2}{12} = \frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}$$

due to the fluctuations which may be expected between different samples of the same large group. The probability that the greater incidence of underweight in our granuloma group is due to such fluctuations is found to be about 33 per cent. One may conclude, therefore, that the increased incidence of underweight in the granuloma group is not large enough to indicate a significant association between granuloma and underweight.

Third, the records of the students with albuminuria were considered. Its incidence was 3.1 per cent greater in the group with granulomata than in the group without (Table 6). Although the difference noted was, in this instance, relatively greater with respect to its standard deviation than in the preceding instance, it does not quite fulfill our requirement for statistical significance, since it is but 1.5 times as great as the standard deviation, there being approximately a 13 per cent chance that such a difference is due to the fluctuations of sampling referred to in the previous paragraph.

TABLE 7.—INCIDENCE OF ELECTROCARDIOGRAPHIC CHANGES IN 160 WOMEN STUDENTS WITH AND WITHOUT DENTAL GRANULOMATA.

	With dental granuloma.		Without dental granuloma.	
	Number.	Per cent.	Number.	Per cent.
Women electrocardiographed	27		133	
Normal tracings	23	85.2	109	82
Tracings showing some departure from normal	4	14.8	24	18

TABLE 8.—MISCELLANEOUS ROENTGEN RAY FINDINGS.

	Students.	Teeth.
Missing teeth	419	896
Impactions	344	686
Residual roots	34	38
Chronic proliferative alveolo-dental periostitis	18	20
Root absorption	9	9
Condensing osteitis	7	7
Chronic rarefying osteitis with cyst formation	4	7
Horizontal absorption of alveolar process	3	3
Chronic rarefying osteitis with suppuration	2	2
Pulp nodules	1	3
Calcification of pulp	1	1
Hyperplasia of cementum	1	1
Fracture	1	1

Finally, the records of 160 women students, who had had electrocardiograms made as part of their routine examination, were analyzed with respect to the presence of granulomata. They were divided into two groups, normal and those departing in some respect from the normal. The latter group was composed of girls whose *Q-R-S* or whose *T* waves were below the accepted standards in Leads I or II, or both, who showed left axis deviation or who exhibited premature contractions. No evidences of grave myocardial damage were found in the group. An analysis of this

group showed that the incidence of electrocardiographic abnormalities was slightly greater in the group without granulomata than in the group with granulomata (Table 7). This result does not support the supposition that in these students granulomata produced electrocardiographic variations from the normal.

In addition to the presence of caries and dental granulomata a number of other dental conditions shown in Table 8 were revealed in the roentgenograms. From the standpoint of systemic disease, chronic rarefying osteitis with suppuration is the most important. This condition may result in osteomyelitis of the jaw, Ludwig's angina, and even fatal bacteremia, though none of these complications occurred in either of our 2 students.

Discussion. The data here presented were secured almost exclusively from youthful persons (Table 1), and should not be regarded as applicable to elderly individuals. While these data offer no support for the view that dental infection causes rheumatism, chorea, valvular heart disease, or electrocardiographic abnormalities in these vigorous young college students, yet, if the body resistance should be lowered by exposure, hardship or advancing years, it is possible that such might be the case. It is also conceivable that granulomata and other dental infections may, like syphilis, lie dormant for many years, finally to arise and smite their victims in later life. It would seem the part of wisdom, therefore, to treat these dental infections as potentially dangerous. This can often be done without the extraction of the affected teeth, it having been demonstrated that the majority of granulomata can be successfully treated through the root canal.³³ The wholesale removal of devitalized teeth and teeth with granulomata is certainly without justification in healthy young individuals such as comprise the present study.

Summary. 1. The literature upon the relationship of dental infection and systemic disease is reviewed.

2. The results of 883 routine medical and dental examinations, including complete dental Roentgen rays, are reported.

3. The Roentgen ray was found to be of great assistance in revealing caries, the latter being present in 83 per cent of the entire group.

4. Chronic rarefying osteitis with granulation tissue (the so-called blind dental abscess) was revealed in 19.8 per cent of the group. It often occurred with underweight and with albuminuria, but no statistically significant association could be demonstrated. It was not associated with rheumatism, chorea, and heart disease.

5. In 160 women students there was no association between the presence of chronic rarefying osteitis with granulation tissue and electrocardiographic abnormalities.

6. Several other roentgenologic abnormalities were found, the most common being impactions and residual roots.

7. The importance of routine dental roentgenograms as part of a thorough physical examination is emphasized.

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TRANSFUSION SYPHILIS.

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RECENTLY Polayes and Lederer¹ reported a case of a child, aged 17 months, who had been infected with syphilis by blood transfusion, and collected 11 such cases from the literature. In addition to the reports cited by these authors, Fordyce² refers to a young girl who

had been infected in this way. Her brother, whose blood was used for the treatment of her anemia, was found to have been in the second incubation period of the disease at the time of the transfusion and in due course of time she had developed a secondary rash

On account of the relative infrequency of such published reports, it seems worthwhile to record the following:

Case Abstract. CASE 1.—Mrs. M. J., an undernourished negress, aged 34 years, presented herself to our dispensary on February 2, 1931, complaining of enlarged cervical glands. She stated that in October, 1930, after a miscarriage followed by severe hemorrhage and anemia, she had been given a transfusion of blood at another local hospital, her sister serving as donor.

When first seen the patient complained of severe headache, which she said had been present since the transfusion. Two weeks later she returned to the dispensary with a generalized corymbose papulopustular eruption. Her blood showed a strongly positive Wassermann reaction. Careful examination revealed no genital or extragenital lesion on either the patient or her husband. The husband's blood gave an entirely negative Wassermann reaction.

The records of the hospital at which the transfusion was given showed that while the donor's blood had been typed, a Wassermann reaction had not been done. After considerable difficulty we induced the obviously reluctant donor to submit to a blood test and the Wassermann reaction was found to be strongly positive.

While her eruption was still present, the patient was presented at a meeting of the Cleveland Dermatological Society with general agreement as to the diagnosis. In the discussion, verbal report was made of two other instances of transfusion syphilis, while a paper read later to a small medical group elicited mention of 4 additional cases. At the first meeting, Dr. H. T. Phillips, of Wheeling, West Virginia, referred to a threatened malpractice suit, which had been settled out of court, because of a syphilitic infection as a result of transfusion.

CASE 2.—In 1929, I was asked to testify about a syphilitic infection allegedly produced by transfusion. It appeared that the patient had been brought to a local hospital 2 years before in a state of severe shock from postpartum hemorrhage. The attending obstetrician had used the patient's brother-in-law as a donor after obtaining a denial of venereal infection. The urgency of the emergency did not permit waiting for the results of a Wassermann test and the patient's husband was not in a suitable blood group. Three months later the patient appeared with a secondary syphilis. In the meantime, a Wassermann reaction had been done on the donor's blood, which was alleged to be positive. I did not have the opportunity to see the patient and the case was soon after stopped for legal reasons. The defense attorney informed me that there were no cases on record of malpractice suits on this score.

Accidents of this sort would introduce a nice question of justice, especially when it is remembered that transfusion is often carried out as a life-saving measure under emergency conditions and that any available donor may have to be used, relying solely upon the denial of venereal infection. Shall the medical attendant save the

patient's life by transfusing blood from an apparently suitable donor at the risk of syphilitic infection or shall he let the patient die because of inability to secure a Wassermann-negative donor in the emergency and fear of possible syphilitic infection? Is the physician not taking every reasonable precaution in a desperate emergency when he attempts to exclude syphilis by questioning the donor and examining the surface of his body and the oral cavity for evidence of healed or active lesions when the condition of the patient is so desperate that time cannot be lost in securing a donor with a negative Wassermann reaction or in having one done on the available donor?

The microprecipitation methods devised by Kline³ would seem to offer the clinician ready assistance, and his finger blood precipitation test with "exclusive test antigen" should be especially useful when little time is available, judging by the results obtained by Eller and Rein.⁴

In reviewing the reported cases, it is evident that the time elapsing between transfusion and the appearance of the eruption, ranged from 1 month to 4 months, the longest interval being in the case herewith reported. In the majority, the time was 2.5 months or longer.

A preponderating number of cases were found to be due to family donors, as noted by Polayes and Lederer. The cases which have been recounted here, still further emphasize the necessity for caution in dealing with family donors. It should be remembered that even professional donors, on whose blood negative Wassermans have been obtained periodically, cannot be regarded as entirely safe on that account alone, because of the possibility of a recent venereal infection, and this points to the desirability of at least a careful inspection of the body surface and especially the genitalia, before transfusion, even in professional donors with repeated periodic negative blood tests.

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OBSERVATIONS REGARDING KIDNEY FUNCTION TESTS IN ACUTE NEPHRITIS.

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It has been maintained that kidney function tests are of little or no value in acute nephritis, because when performed some time after the onset of the disease they generally show normal results,

whether the disease is cured or it has become chronic (Lundsgaard¹). Hence we are in a difficult position when in a given case we are to settle the question between a cured acute nephritis and a chronic nephritis. The common chemical and microscopic examination of the urine does not give any definite clue, because on the one hand acute nephritis according to Volhard² may be cured in spite of a persisting albuminuria, which may not disappear for several years, and on the other hand the complete disappearance of albumin, casts and red blood corpuscles from the urine does not necessarily mean that the nephritis is cured. Donath³ has observed 3 cases in which the Volhard concentration test showed pathologic results for some time after the urine had become normal and later became normal. Such cases do not seem to be frequent, but it must be remembered that it has not hitherto been common to perform functional tests in cases of acute nephritis when the urine has become absolutely normal.

These facts, that the nephritis may be cured in spite of persisting albuminuria and that the kidney function may be decidedly deficient in spite of the disappearance of all pathologic components of the urine, render the functional tests necessary in acute nephritis, and the best and finest will here be desirable. One cannot be sure that cases like Donath's would not have developed into chronic nephritis if treatment had been stopped, for instance 1 or 2 weeks after the urine had become normal. The ideal must be to treat these patients until they have both normal urine and normal function.

In this article I shall try to set forward the experiences with functional tests in 25 cases of acute nephritis. Almost all these cases have been followed with repeated functional tests from the onset of the nephritis. The functional tests employed have been the Volhard-Strauss test and chiefly the creatinin test in the form given by Rehberg⁴ and the author, by which the "creatinin clearance" is determined, *i. e.*, the amount of blood plasma cleared of creatinin per time unit. For reasons discussed in earlier papers we consider the value $\frac{\text{Cr U \%}}{\text{Cr P \%}} \times V^* = F$ (*i. e.*, the amount of fluid filtered in the glomeruli per minute equals the amount of filtrate or the filtration rate). For further description of the method I must refer to earlier papers; I only want to add that the creatinin test can be employed without causing any harm to the patient, even in quite recent cases.

The Volhard-Strauss test has been performed in the manner described by Volhard. As this test involves drinking of considerable water, which may be harmful to the patient, it has not been done at a very early stage of the disease. As has been stated by several authors, the result of the water excretion and dilution test

* Cr U% means the concentration of creatinin in the urine of a given space of time; Cr P%, the concentration in the blood plasma at the same time, and V, the diuresis for this time.

is to a large extent depending on extrarenal factors. It is customary to put these patients on a rather limited fluid intake; this alone suffices to make the water and dilution test illusionary. The results of this part of the Volhard-Strauss test have, therefore, not been taken into consideration. The concentration test is, however, of considerable importance.

Further the blood urea has been determined at short intervals and the daily diuresis and specific gravity of the urine has been determined.

The material comprises 25 patients with acute glomerular nephritis treated in the Blegdamshospital in Copenhagen (fever hospital). They have, as already stated, almost all been followed from the onset of the nephritis. Most of the patients were sent to the hospital for an acute infection (scarlet fever, angina, etc.) and got nephritis while in hospital. Several of the patients were children. The normal amount of filtrate in these is, of course, different from that of adults. The minimum value can, however, be determined from the surface area of the child, which is easily computed by means of Du Bois⁵ or Benedict and Talbot's⁶ tables. I have shown that the minimum filtrate per square meter is 60 cc. per minute, the average being 83.3 cc. per minute.⁷

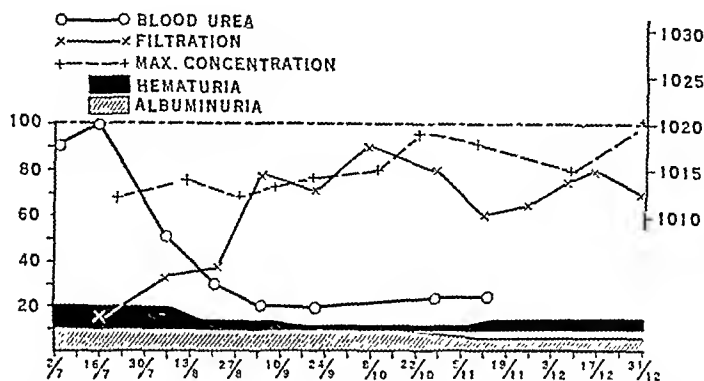
Acute nephritis may run a different course. There are three possibilities: (1) The disease passes into chronic nephritis (Volhard's second stage); (2) the disease is cured, the pathologic processes are entirely stopped and completely repaired (*restitutio ad integrum*); (3) in some cases albuminuria and hematuria may persist for some time and then disappear. Volhard speaks of "Defektheilung" or "Restalbuminurie." Even if in these cases a *restitutio ad integrum* has not taken place, Volhard is of opinion that no further development of the alterations in the kidneys which is the cause of these pathologic excretions takes place; this can, however, only be ensured by observation for a long time.

I will, by means of illustrating examples out of my material, endeavor to show the value of function tests in judging the course of a given case of acute nephritis and in settling the question whether the disease is cured or not.

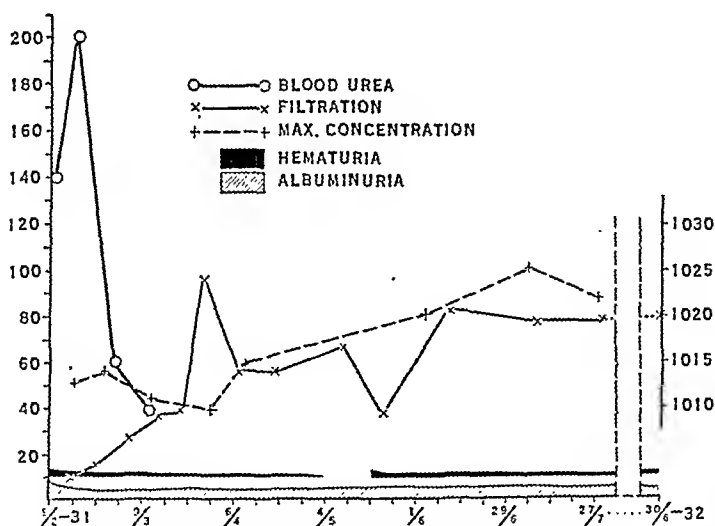
First, I want, however, to call attention to the fact that in most of these cases the albuminuria (positive Heller's test) disappears before the microscopic hematuria. The urine was examined for albumin once or twice a week and microscopic examination was carried out once a week. Only in 1 out of 25 cases did the erythrocytes disappear before the albumin; this case will be referred to later. In 2 cases the disappearance seemed to take place simultaneously, and in 19 cases the albumin first disappeared, in 1 case even 4 weeks before erythrocytes. Two cases became chronic and 1 case was regarded as recovered with "Restalbuminurie."

Curves 1 and 2 give the function tests in the 2 cases which became

chronic. The first curve is from a young man, aged 17 years, who had always been well until 2 days before entering the hospital, when he got a rather severe angina. On entrance to the hospital on June 26, 1930, he had marked albuminuria and hematuria, rather high blood urea and a very low filtration (14 cc. per minute



CURVE 1.—Acute nephritis developing into chronic. The function does not become normal. — — — means the lowest normal filtration rate for a person of the patient's size.



CURVE 2.—Acute nephritis developing into chronic. Concentration power becomes normal. Filtration rate remains too low.

on July 16), with impairment of concentration power (maximum concentration 1013). His blood urea became normal rather quickly (within 5 weeks) and function improved; but not until after some 8 weeks did the filtration rise rather sharply to 80 cc. per minute and the concentration power to about 1015. But albuminuria and microscopic hematuria persisted and both the filtration rate and

the concentration power remained low even 6 months after the onset of the nephritis.

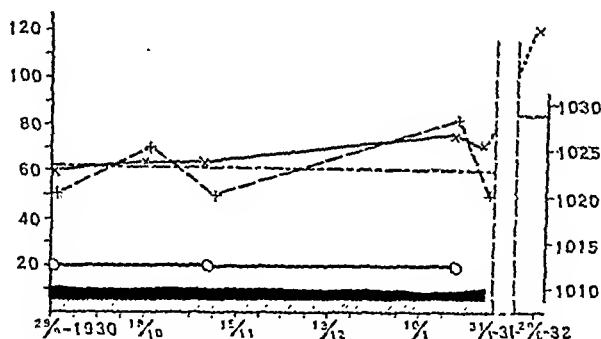
Curve 2 is derived from a young woman, aged 19 years, who never had been ill until she got erysipelas of the face (January 15, 1931), and was sent to the hospital. On admission the urine did not contain albumin, but on January 17 the urine was bloody. As it is seen from the curve the filtration was very low (9.5 cc.), the blood urea very high. Not until 2 months after the onset of the nephritis did a considerable rise of the filtration take place. The albuminuria and microscopic hematuria, however, still persist and the filtration test remains too low even 1 year and 5 months after the onset of the nephritis. In this case the concentration power became normal some 6 months after the onset of the nephritis. The filtration test thus seems to be more delicate than the concentration test. I shall refer to this later.

It will be observed that in both these cases the functional impairment is severe and a considerable improvement did not occur until relatively long time after the onset.

Curve 3 shows a case where the diagnosis "Restalbuminurie" was probable and later confirmed by reexamination. It is from a boy, aged 9 years, who in November, 1929, had got angina and a consecutive acute hemorrhagic nephritis. Functional tests were not carried out until 10 months after the onset; hematuria and albuminuria were then still present. Filtration at that time was at the lowest normal level. It slowly improved, and when the boy was examined again on July 1, 1932, 2 years and 8 months after the onset of the nephritis, function was perfectly normal (128 cc.) and no albumin, erythrocytes or casts were to be found in the urine. In this case the diagnosis "Restalbuminurie" or "Defektheilung" proved to be right, but I want once more to emphasize that this diagnosis can only be accurately determined by observations over a long time.

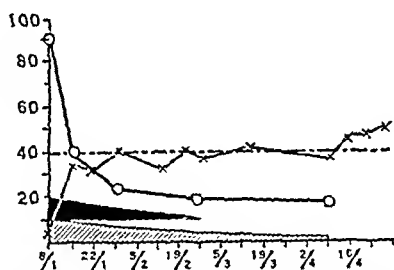
The next curve (Curve 4) shows this. The diagnosis "Restalbuminurie" was very tempting, but the filtration test shows that the nephritis was not cured until 4 to 5 weeks *after* the cessation of the microscopic hematuria. The patient was a little girl, aged 4 years, who had been ill for 2 months before entrance to the hospital. Albumin had been found in the urine after a cold. The urine was free from albumin when she got up 4 days before entering the hospital, but she immediately became ill again with very bloody urine and was sent to hospital on January 4, 1931. She was azotemic and the filtration rate was very low but rose rapidly. The blood urea quickly became normal. On February 26 no blood corpuscles were to be found in the urine but albuminuria persisted. The filtration rate was at the lowest normal level or a little lower. On April 9 the albuminuria stopped and the filtration rate showed a marked rise to values definitely above the lowest normal level.

In this case the functional test with creatinin proved to be of value in the differential diagnosis between "Restalbuminurie" and still existing nephritis.



CURVE 3.—"Restalbuminurie"—disappeared 2 years and 8 months after onset.
 - - - - - lowest normal filtration rate.

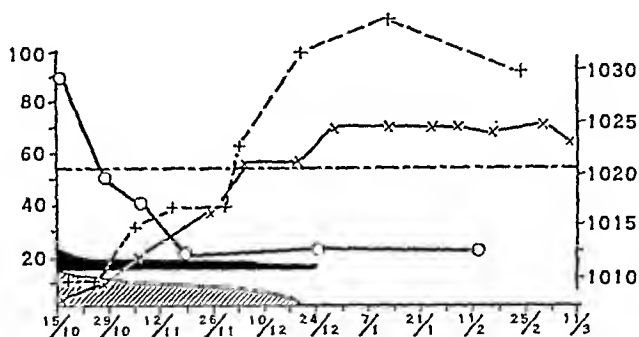
As mentioned before, albuminuria most commonly disappears before the microscopic hematuria. Function as determined by means of the creatinin test often becomes normal at the same time as the microscopic hematuria disappears. Curve 5, from a case of scarlet fever nephritis in a boy, aged 5 years, is an example of this.



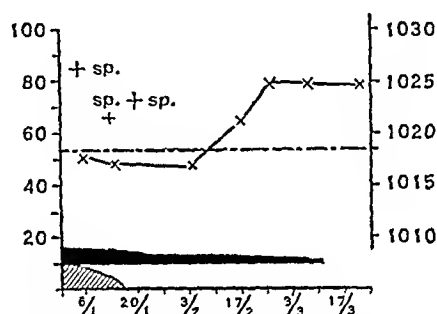
CURVE 4.—The filtration rate does not become normal until 4 weeks after the disappearance of red blood cells in the urine simultaneously with the disappearance of the albuminuria.

The concentration test gives normal results before the filtration rate is normal. A further example has already been given in Curve 2. Curve 4 is an example of a course which only was seen once in 25 cases, the erythrocytes disappearing before the albumin and function becoming normal simultaneously with the disappearance of the albuminuria. Another course which is very uncommon is shown in Curve 6, derived from another case of scarlet fever nephritis in a girl, aged 8 1/2 years. In this case the albumin disappeared and a couple of weeks later the filtration rate became normal, but the microscopic hematuria persisted for another couple of weeks. Such a course I have only seen once. But a course which is by no means

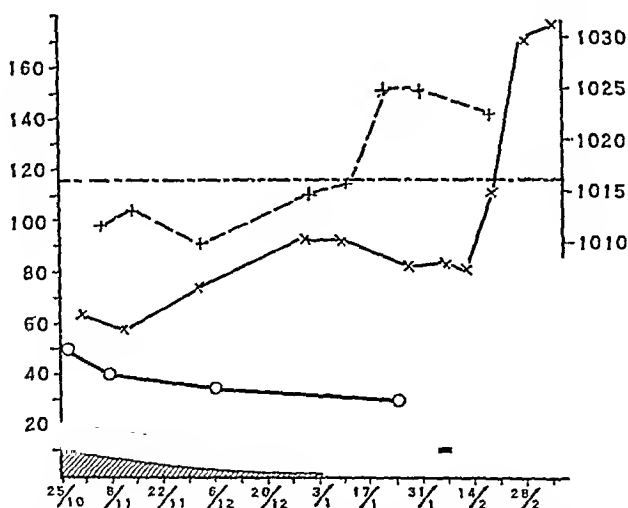
uncommon is seen in the 3 following curves. The first (Curve 7) is from an adult woman, aged 27 years. She came into hospital



CURVE 5.—The filtration rate becomes normal at the time when the hematuria disappears—a common course. Concentration power normal about 4 weeks before normal filtration has been reached.



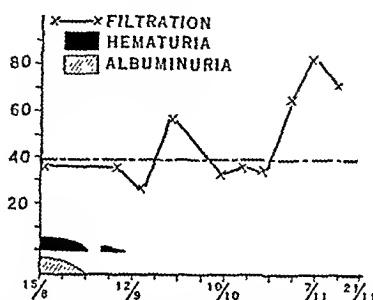
CURVE 6.—The filtration rate becomes normal before the hematuria disappears; sp. = spontaneous specific gravity of the 24-hour urine.



CURVE 7.—The filtration rate does not become normal until 14 days after erythrocytes has disappeared from the urine. The concentration power is normal 1 month before the filtration rate becomes normal.

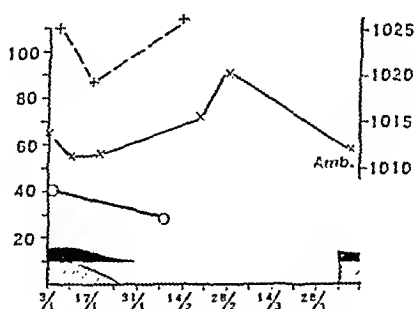
with an *angina phlegmonosa* without symptoms or signs of renal involvement, but a few days after admission albumin and blood

was found in the urine. In this case the albuminuria disappeared first, the erythrocytes disappeared 14 days before the filtration rate became normal. Also it is worth mentioning that the concentration test showed too low values after the disappearance of the albuminuria; but the concentration power became normal 1 month before the filtration rate. Again it is seen that the concentration test is a much coarser test than the filtration test.



CURVE 8.—Intermittent course with relapse of the function to values below normal after disappearance of red blood cells from the urine.

Curve 8 is derived from a boy, aged $4\frac{1}{2}$ years, with scarlet fever nephritis which began on August 10, 1931. The albuminuria disappeared very quickly (August 29) and the microscopic hematuria was very slight. In spite of very careful and repeated examinations erythrocytes were found in the urine, the last time on September 2, but the filtration rate did not become normal until some time



CURVE 9.—Relapse after discharge with normal urine but too low filtration rate. Reappearance of albuminuria and hematuria.

between October 23 and 31. This case further shows that the filtration rate may show rather large variations during the course of the acute nephritis. Improvement and relapses in the function occur in this case, and they are seen not to be concomitant with variations in the sediment.

These 2 cases show the great value of the creatinin test in acute nephritis. It is generally accepted that acute hemorrhagic nephri-

tis can be regarded as cured when albuminuria and microscopic hematuria have definitely stopped. This can no longer be regarded as a safe assumption, when it is beyond doubt that the function may be well below normal at a time when all pathologic findings have disappeared from the urine. That neglect of the still impaired function may cause serious damage to the patient is seen from the following case (Curve 9). The patient, a woman, aged 32 years, entered the hospital on December 7, 1930, with *angina phlegmonosa* with several abscesses. On December 30 acute hemorrhagic nephritis set in. The albuminuria ceased on January 26, 1931, the hematuria on January 31; in 2 later microscopic examinations of the urine nothing abnormal was found. The filtration tended to rise but did not get normal (84 on February 28). On March 1 the patient wanted to leave the hospital. On March 31 she was re-examined, the filtration rate was lower (58) and the urine contained albumin and microscopic blood. Of course, one cannot prove that this relapse would not have occurred if the patient had not been permitted to get out of bed and leave the hospital; but to me it appears very probable that it might have been avoided if the rising tendency of the function, which is shown by the tests on February 21 and 28, had been allowed to continue. It is beyond doubt that the function of the kidney in normal subjects is better in the lying than in the upright position. This has been shown to be correlated with differences in the colloidal osmotic pressure of the plasma in these positions. The bearings of these facts on pathologic conditions have not been investigated, but it is probable that the effect of the position here is still more obvious. One can say that it is desirable to keep the patients with acute nephritis in bed while symptoms of a pathologic state are present, and the facts just referred to may give some understanding as to why the pathologic processes in the kidney are influenced by the patient's lying in bed or getting up.

The case just referred to is a still further example of the concentration test showing normal value when the filtration rate is too low. In these cases I have never seen the creatinin test become normal before the concentration test, and as has already been pointed out the concentration test may be normal several weeks before the filtration rate becomes normal.

It must be pointed out that values marked in the curves as the lower normal level are minimum values for normal persons with a given surface area. The values which patients must reach before I regard their filtration rate as being perfectly normal lie above this minimum value. This is because continued observation has shown that the filtration rate has risen to a higher level. Not until this level has been reached have I considered the filtration rate as normal. This does not affect the conclusion that the microscopic hematuria may disappear several weeks before the filtration rate can be

regarded as normal and that the concentration test may show normal results long before the filtration rate is within the normal zone.

In 3 cases the filtration rate has risen to values much above the average normal level and then fallen a little again. I do not know the significance of this fact. It may be due to a low colloidal osmotic pressure of the plasma, as this tends to enhance the filtration in the glomeruli. These patients were treated with a low protein diet and the protein restriction was lessened when function grew better. The cases were the following:

CASE 1.—A girl, aged $3\frac{3}{4}$ years, had scarlet fever, about Christmas, 1930, and nephritis, beginning January 5, 1931. Urine still contained albumin and erythrocytes, January 19; no pathologic contents on January 31 and several times later. *Filtration rate*: January 10, 29 cc.; January 15, 23; January 22, 47; January 30, 47; February 6, 34; February 20, 34; March 7, 66; March 14, 46; March 20, 46. Her weight was 15.6 kilos. Surface area (Benedict-Talbot), 0.67 sq. m. Minimum filtration rate, 40 cc.

CASE 2.—A girl, aged $3\frac{3}{4}$ years, the twin sister of Case 1, had scarlet fever and nephritis at the same time as Case 1. Urine still contained albumin and erythrocytes on January 19. On January 31 no albumin, but a few erythrocytes, and again on February 6. On February 13 and several times later no pathologic contents were found. *Filtration rate* on January 10, 20; January 15, 29; January 22, 45; January 30, 43; February 6, 38; February 20, 28; February 28, 35; March 7, 60; March 14, 63; March 20, 56; April 4, 49. Her weight was 15 kilos. Surface area (Benedict-Talbot), 0.657 sq. m. Minimum filtration rate, 40 cc.

CASE 3.—A boy, aged 3 years, had scarlet fever, November 15, 1930, and nephritis, December 4, 1930. The urine on January 19 contained no albumin, but 8 to 10 erythrocytes in each microscopic field; on January 26 a few erythrocytes; on January 31 and several times later no pathologic contents were found. The filtration rate was on December 11, 14 cc.; December 19, 36; December 31, 15; January 8, 21; January 15, 29; January 22, 21; January 30, 30; February 14, 55; February 28, 40; March 4, 42. His weight was 14.2 kilos. Surface area (Benedict-Talbot) was 0.62 sq. m. Minimum filtration rate, 33 cc.

Addis and coworkers⁸ maintain that the amount of erythrocytes and casts in the urine is a valuable index of the activity of the pathologic process. In these cases no countings of erythrocytes and casts were made. But cases like the 3 quoted in which by several careful examinations no erythrocytes and casts were to be seen, the function being still decidedly below the normal level, to my mind make it doubtful if this quantitative method is absolutely reliable. At any rate it does not seem justifiable to consider the pathologic process as inactive at this stage. The case observed in which relapse occurred speaks strongly against such a standpoint. It is a well-established fact that patients who have gone through an acute nephritis and whose urine had become perfectly normal later on may show all signs of chronic nephritis.

Vollhard^{2b} writes (page 1303): "The disease can apparently heal and only after a considerable or even lengthy period lead to kidney insufficiency." And quite in accord with this, Siebeck⁹ writes:

"There are some patients who after the most careful and expert care are discharged as 'cured' and later, perhaps after years, succumb to a typical contracted kidney." These facts seem to me to make it necessary to treat these patients whenever possible until both chemical and microscopic examinations of the urine and function tests (and the most sensitive tests are desirable) show normal results. Only when this is done can it be said that everything has been done to avoid chronic nephritis as a result of an acute nephritis.

The fact that some follow-up researches often show or appear to show a rather favorable prognosis for acute nephritis does not alter the desirability of being as certain as possible of the acute nephritis being cured when treatment is stopped. Hansborg¹⁰ has reexamined patients with scarlet fever nephritis and shown that relapses and cases that had become chronic could not be found. On the other hand, reexaminations of cases of war nephritis both from English and German authors (Hume and Natras,¹¹ Gros¹²) show that at least one-third of the cases become chronic, while only about half of all cases have completely recovered. Tallermann¹³ has examined 27 cases of acute nephritis in children; of these 2 died and 18 are regarded as recovered, 4 show evidence of renal damage. As most of his patients were discharged when the urine still contained red blood corpuscles and albumin this might be considered as an evidence that rigorous treatment until normal urine and normal function is reached is not necessary. But, still, 4 patients with renal damage out of 25 patients discharged is not quite a small number; and further, 8 patients could not be considered as "completely recovered," 2 being considered as "probably completely recovered" and 6 as "recovered." Of these 8 patients 7 had albuminuria on reexamination, 1 had only a slightly impaired phenolsulphonephthalein excretion but no albuminuria. As the function tests used in these examinations (blood urea, urea concentration and phenolsulphonephthalein) are very coarse tests, marked renal damage cannot be excluded in these cases. In other words, only 13 patients out of 25 can safely be regarded as being cured. Tallermann's material seems to me to speak strongly for the necessity for the rigorous treatment of patients with acute nephritis.

The ideal result to attain is that the patient has no albuminuria, that the centrifugate from the urine does not contain abnormal elements and that the function as judged by the creatinin test and the concentration test is normal. That we sometimes cannot reach this ideal is obvious. In such cases where albumin and erythrocytes do not completely disappear it seems to me that the finding of a normal filtration rate permits a favorable prognosis and to some degree speaks in favor of the diagnosis "Restalbuminurie" and against chronic nephritis.

Is a *topical diagnosis* by means of the creatinin test possible?

It is well known that the concentration power may be maintained in acute nephritis. I have shown several cases in which the concentration power is regained before the filtration rate as determined by the creatinin test becomes normal. The case illustrated in Fig. 9 is a good example of the fact that the concentration power at the onset of the acute nephritis may be normal while the filtration rate is markedly impaired. I will give some further examples:

CASE 4.—Poul H., aged 5 years, had scarlet fever, September 29, and nephritis, October 15. On October 15 the 24-hour urine had a specific gravity of 1021; on October 16 the filtration rate was 16 cc. per minute; on October 17 the 24-hour urine had a specific gravity of 1019. His filtration rate rather quickly went up again, on October 29 it was 45 cc.; his normal value was about 55 cc.

CASE 5.—Poul B., aged 10 years, had scarlet fever on September 15 and nephritis on October 5. October 7, specific gravity, 1025. October 8, filtration rate 25 cc., specific gravity 1021. October 9, specific gravity 1020. His normal value for the filtration rate was about 80 cc.

It should be emphasized that none of these urines contained so much albumin that it could affect the specific gravity.

I have not seen the concentration power maintained in cases in which the filtration rate was very seriously impaired (below 10 cc. per minute).

Vollhard explains the fact that the concentration power may be maintained in acute nephritis according to his theory. He says that the tubuli are able to excrete solids to a normal extent while the capsules on account of ischemia cannot excrete water. The low creatinin clearance combined with maintained concentration power must mean either that creatinin is excreted through the capsules—and this is not in accord with the views of Vollhard—or that the power of the tubules to excrete creatinin alone and not other solids is impaired, which is absurd. It is difficult to explain this discrepancy between the creatinin clearance and the concentration power in any other way than by assuming that the creatinin is filtered through the capsules. If the filtration rate is very seriously impaired or if it has been damaged for a long time it is no wonder that the concentration power is found lowered. That is on account of the anatomical facts. The tubules may atrophy from inactivity, and further it must be kept in mind that by far the largest amount of blood which goes to the tubules passes the glomeruli. When the arteries do not let the blood pass on account of either functional ischemia or ischemia from obturation of the capillaries, the blood supply of the tubules must suffer and so also the function of the tubules. Hence the lowered creatinin clearance must mean lowered filtration rate in the capsules—a suffering of the capsules—the lowered concentration power that the tubules are suffering. When the concentration power is maintained while the filtration rate is normal this means that the capsules are seriously involved by the morbid

process while the tubules are free or relatively free. Thus in acute nephritis a topical diagnosis by function tests is possible to a certain extent. In chronic nephritis this possibility does not exist because both the capsule and the tubule—the whole “nephron”—are and must be suffering.

Is it possible to draw any prognostic conclusions from the degree of the functional impairment? It is evident from my material that even when this has been very large the restoration may be complete (see for instance the case illustrated in Curve 4 in which the filtration rate was only 10 per cent, and the case illustrated in Curve 5 in which it was only about 8 per cent of the normal value.) But if the 2 cases which became chronic (Curves 1 and 2) are analyzed it will be seen that both of them show a very marked functional impairment and this very severe damage lasts for a long time. In the case illustrated in Curve 1 the filtration rate 8 weeks after the onset is still about 30 cc. per minute, *i. e.*, only 30 per cent of the normal value; not until 9 to 10 weeks after the onset a marked rise occurs. In the other case also more than 2 months elapsed after the onset of the nephritis before a marked rise of the filtration rate set in; 9 weeks after the onset the filtration rate is only 30 per cent of the normal.

This very long duration of the serious functional impairment has not been seen in the other cases. Compare, for instance, the case from Curve 5, just quoted, in which the damage was severe. Here the filtration rate 3 weeks after the onset has already risen to more than 50 per cent of the normal. And in the case from Curve 4, also with a very severe damage (down to 10 per cent) the rise is still sharper so that the filtration rate only 10 days after the onset has risen to about 85 per cent of the normal. In other cases the rise is less sharp but then the damage will be seen to have been less serious.

My impression is that when the functional impairment is large and does not recede within 4 to 6 weeks, this means that the danger of the nephritis becoming chronic is very menacing. If the filtration rate reaches values of about 50 per cent within 4 weeks the prognosis seems to be good, even if the filtration rate at the beginning has been very low.

As it will be readily seen from the curves, the blood urea rapidly falls when the patients get under treatment. Of course, the raised blood urea means that the kidney function is much impaired, but as it may be normal at a time when the function is still very far from being normal it is not of any value at the time when improvement is going on and it is to be determined if the function has got normal. The value of the blood urea determination as a kidney function test has been spoken of in a former paper to which the reader is referred.⁴

The blood pressure is not—at any rate not directly—dependent on the kidney function. Nevertheless it has been used as a guide

for treatment. Volhard considers it unnecessary to keep the patient in bed when the blood pressure has fallen to normal. As it will be understood, I cannot agree with this standpoint. The blood pressure has in all these cases fallen to normal long time before the function has got normal. It cannot be denied that the impaired function must be a less coarse sign of the morbid process in the kidneys than the blood pressure rise. This may be influenced by several extrarenal factors and further it is by no means known to be produced by the morbid process in the kidney.

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THE KETOGENIC DIET IN NORMAL INDIVIDUALS: A BIOCHEMICAL INVESTIGATION.

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DURING the last 10 years a number of reports have appeared on the good results of treatment of epilepsy and asthma by the ketogenic diet, especially in American journals, by Wilder,¹² Peterman,⁵ Talbot, Metcalf and Moriarty,⁷ Lennox and Cobb,⁴ Helmholtz² and others.

Nobody, however, so far as we are aware, has made a complete examination of the changes in the acid-base balance of the blood under the influence of this diet, though Weymuller and Schloss¹¹

reported the results of some partial examinations of the blood of normal and asthmatic children.

The Ketogenic Diet. Wilder,¹² of the Mayo Clinic, noted that certain epileptic patients improved with starvation and the consequent acetonuria, and he suggested the possibility of the use of high fat diets in the treatment of epilepsy, a method which has been steadily developed, until now it is generally accepted as one of the best of the known methods of treatment. The well-known effect of acidosis in producing a relaxation of smooth muscle would also suggest its use in such conditions as asthma.

Briefly the method consists in increasing the $\frac{\text{fatty acid}}{\text{dextrose}}$ (or $\frac{\text{ketogenic}}{\text{antiketogenic}}$) ratio in the diet. The value of this ratio is calculated from the formula $\frac{0.44P + 0.9F}{C + 0.56P + 0.1F}$ since proteins, and to a small extent fats, contain ketogenic and antiketogenic substances. In ordinary diets the value of the fatty acid-dextrose ratio is about 1 to 2. With patients this ratio is gradually increased to 1 to 1, 2 to 1 and, finally, 3 to 1 or even more. Ketone bodies appear in the urine within the first 2 or 3 days, and improvement is often noted within the first week. Many cases, however, appear to be refractory to treatment, and in asthma, at any rate, adults are not so favorably affected as children. It occurred to us that a complete examination of the blood as regards acid-base changes might throw some light on this problem, since variations in the acid-base balance, though probably not the cause of epilepsy and asthma, accompany and experimentally influence these diseases.

Methods. Three healthy women students, aged from 21 to 23, volunteered to undergo the examination. For 18 days they adhered rigidly to the ketogenic diet, under the direction of Miss Mabel Flanley, B.S., Consulting Dietitian, of Seattle, Washington. Blood examinations were made in each before commencing the diet, on the 9th and 18th days and again 18 days after return to normal diet, thus making 4 blood examinations in all.

From the fasting subject, at 9 A.M., 30 cc. of blood were drawn without stasis from the median basilic vein into a large Record syringe containing a standard amount of potassium oxalate as anti-coagulant. The whole blood was then "arterialized" by bringing it into equilibrium with alveolar air, using the method described by van Slyke.⁸ A portion was next transferred under oil, without loss of CO₂, to a centrifuge tube, centrifuged for 1½ hours, and the plasma separated. The following were then determined:

- (a) The chlorid content of both whole blood and plasma (method of van Slyke⁹).
- (b) The carbon dioxid combining power of both whole blood and plasma (van Slyke⁸).
- (c) The relative volumes of corpuscles and plasma in the whole blood (hematocrit method).

From the above a simple calculation gave us:

(d) The chlorid content per 100 cc. of red cells.

(e) The carbon dioxid combining capacity per 100 cc. red cells.

All estimations were made in duplicate, and the figures for red cell volumes per cent are each the average of 4 determinations. We are, of course, aware of the difficulties in determining the true red cell volume per cent by any hematocrit method, as has been well shown by Ponder and Saslow.⁶ As their method requires 35 cc. of blood in addition to that required for chlorid and carbon dioxid concentrations, it was obviously undesirable to use their method with our young female subjects. Since, however, we were concerned with showing comparative changes in the blood of each subject at various times, and we used the same method for all (1600 revolutions per minute for 1½ hours in uniform bore hematocrit tubes), we feel, as Ponder and Saslow themselves state, that the hematocrit method may be useful for the determination of relative changes in cell volume. That this method as employed by us may give good comparative results is shown by the straightness of the curves in Fig. 4.

TABLE 1.—MISS B.

Date.	Carbo- hy- drate.	Pro- tein.	Fat.	Cal- ories.	F.A.:G. ratio.	Urine tests.				Wt.	Remarks.
						Rothera.		Lange.			
						A.M.	P.M.	A.M.	P.M.		
June											
16	75	45	195	2215	1.7:1	144	Blood exam.
17	75	45	195	2215	1.7:1	+++	143½	
18	75	45	195	2215	1.7:1	++	++	143½	Very heavy and sleepy
19	75	45	195	2215	1.7:1	++	++++	143½	Very heavy and sleepy.
20	42	45	195	2083	2.1:1	++++	++++	++	++	142½	Very heavy and sleepy.
21	42	45	195	2083	2.1:1	++++	++	141	Headache.
22	32	45	214	2324	2.7:1	+	++	141	
23	32	45	214	2324	2.7:1	++	+	141	
24	32	45	214	2324	2.7:1	++++	++	140½	Blood exam.
25	32	45	214	2324	2.7:1	++++	+	140½	Easily tired.
26	23	48	230	2300	3.0:1	++++	++++	140½	
27	23	48	230	2300	3.0:1	++++	++++	140	
28	23	48	230	2300	3.0:1	++++	++++	139½	Nausea.
29	23	48	230	2300	3.0:1	++++	++++	139½	
30	23	48	230	2300	3.0:1	++++	++++	139½	
July											
1	37	48	230	2500	2.7:1	++++	++++	139	Headache, nausea at night.
2	37	48	230	2500	2.7:1	++++	++	139	More normal.
3	37	48	240	2500	2.7:1	++++	++	139	More normal.
4	Blood exam.

Results and Their Significance. Tables 1; 2 and 3 show details of the diets used, together with urinary tests, and Figs. 1, 2 and 3 show the changes that took place in the blood during the period of examination as regards the concentrations of chlorids and bicarbonate in both plasma and red cells. Unfortunately no observations of urinary pH were made. In all subjects the following blood changes were found: (a) A slight fall of plasma carbon dioxid; (b) a more marked fall of red cell carbon dioxid; (c) a fall in the

ratios $\frac{(\text{CO}_2)_c}{(\text{CO}_2)_p}$ and $\frac{(\text{Cl})_c}{(\text{Cl})_p}$ (there is 1 exception to this, Fig. 1); (d) a fall in the total volume of the red cells.

TABLE 2.—MISS M.

Date.	Carbo- hy- drate.	Pro- tein.	Fat.	Cal- ories.	F.A.:G. ratio.	Urine tests.				Wt.	Remarks.
						Rothera.		Lange.			
						A.M.	P.M.	A.M.	P.M.		
June											
15	78	41	196	2240	1.70:1	++	123	Blood exam.; very tired.
16	78	41	196	2240	1.70:1	++	122	Very hungry.
17	78	41	196	2240	1.70:1	+	++	122	Nausea before breakfast; hungry.
18	78	41	196	2240	1.70:1	+++	+++	121½	Meals difficult to dispose of, especially butter.
19	78	41	196	2240	1.70:1	+++	+++	+++	++	121½	Normal all day.
20	81.9	41	210.6	2390	1.60:1	++++	+++	+++	++	121½	Very tired; nausea; after- noon in bed.
21	81.9	41	210.6	2390	1.60:1	+++	++	121½	Headache all day.
22	46.8	41	210.6	2246.6	2.20:1	++	+++	121	
23	46.8	41	210.6	2246.6	2.20:1	+++	++	120½	
24	46.8	41	210.6	2246.6	2.20:1	+++	++	120½	Blood test.
25	46.8	41	210.6	2246.6	2.20:1	+++	+++	120	
26	33.69	41	224.6	2320	2.75:1	+++	++	119	Normal.
27	33.69	41	224.6	2320	2.75:1	+++	+++	119	Giddiness.
28	33.69	41	224.6	2320	2.75:1	+++	+++	..	Tire easily since on diet; poor sleep.
29	33.69	41	224.6	2320	2.75:1	+++	+++	118½	Hungry all day.
30	38.55	41	228.6	2631	2.60:1	+++	+++	119	Nausea before breakfast.
July											
1	38.55	41	228.6	2631	2.60:1	+++	+++	119	Normal.
2	38.55	41	228.6	2631	2.60:1	+++	+++	119	
3	+++	Blood exam.

TABLE 3.—MISS T.

Date.	Carbo- hy- drate.	Pro- tein.	Fat.	Cal- ories.	F.A.:G. ratio.	Urine tests.				Wt.	Remarks.
						Rothera.		Lange.			
						A.M.	P.M.	A.M.	P.M.		
June											
15	95	42	243	2735	1.60:1	+	—	110	Blood exam.
16	95	42	243	2735	1.60:1	+++	+	+	—	109	Depression.
17	95	42	243	2735	1.60:1	++	+	—	=	110	Sleepy and listless.
18	95	42	243	2735	1.60:1	++	++	+	+	109½	
19	95	42	243	2735	1.60:1	++	++	110	Very tired.
20	54	42	243	2571	2.20:1	++	++	109½	More normal.
21	54	42	243	2571	2.20:1	++	++	..	Normal.
22	54	42	243	2571	2.20:1	++	+++	108	Nausea.
23	40	42	258	2700	2.77:1	++	++	107	Nausea and faintness.
24	40	42	258	2700	2.77:1	++	++	107½	Blood exam.
25	40	42	258	2700	2.77:1	+++	++	107½	Listless.
26	33	42	270	2700	3.10:1	+++	++	107	Tired.
27	33	42	270	2730	3.10:1	++	+++	107	Normal.
28	33	42	270	2730	3.10:1	+++	++++	..	Normal, day; nausea, night.
29	33	42	270	2730	3.10:1	+++	+++	106	
30	33	42	270	2730	3.10:1	+++	+++	106½	
July											
1	33	42	270	2730	3.10:1	+++	+++	107	
2	33	42	270	2730	3.10:1	+++	?	108	
3	+++	Blood exam.

In order to interpret these results we have applied the laws relating to the distribution of chlorid, bicarbonate and hydrogen

ions in blood, which have been worked out, during the last few years, by van Slyke and his fellow workers.¹⁰

According to one of these laws, the ratio of chlorid concentration in cells to chlorid concentration in plasma is equal to the ratio of

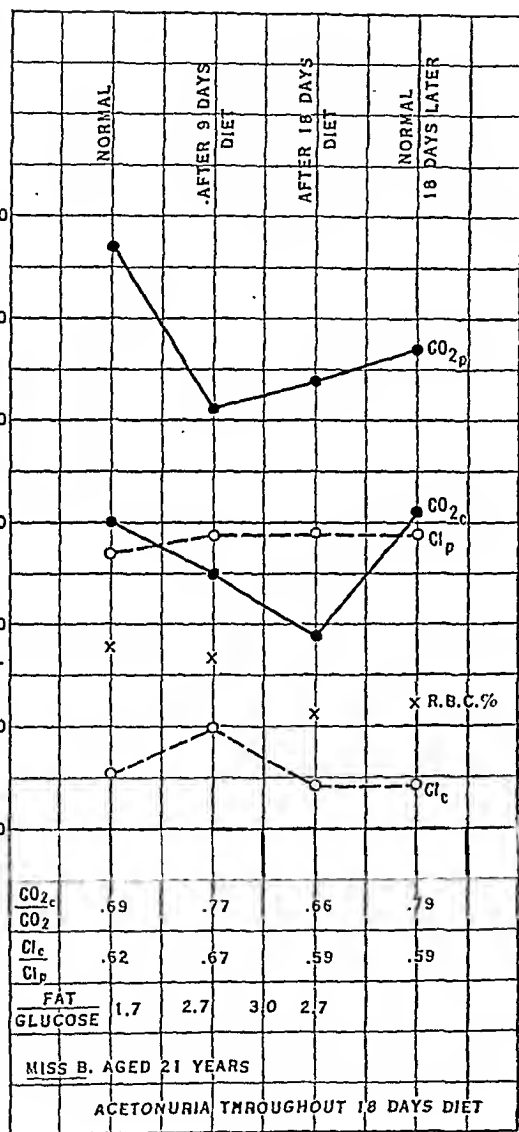


FIG. 1

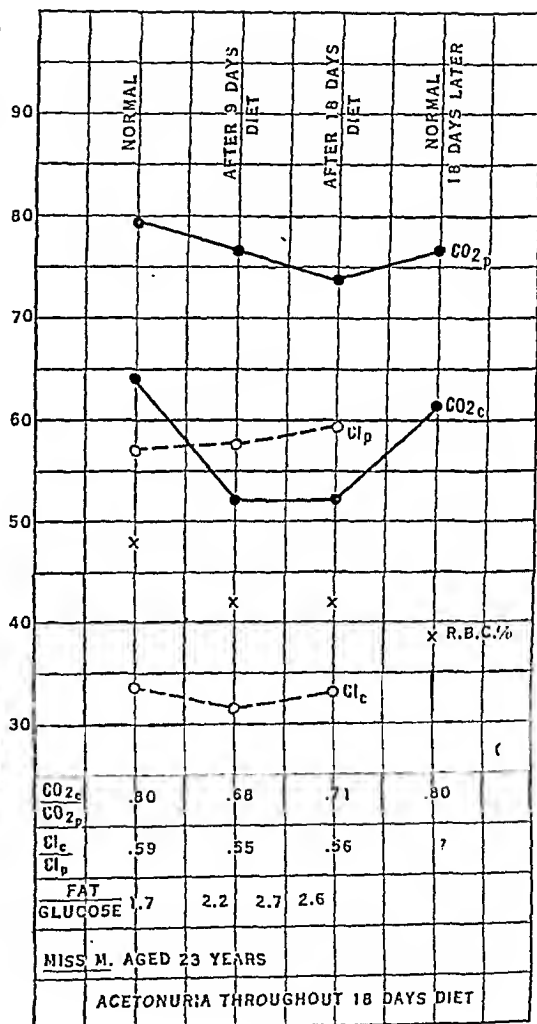


FIG. 2

bicarbonate concentration in cells to bicarbonate concentration in plasma. The numerical value of this ratio is determined by the concentration of base-binding hemoglobin in the red cells, which in turn depends on the hydrogen-ion concentration of blood. Further,

the value of the ratio rises with increase of hydrogen-ion concentration, or acidemia, and falls in alkalemia. These laws may be expressed thus:

$$\frac{(Cl')_c}{(Cl')_p} = \frac{(HCO_3')_c}{(HCO_3')_p} = \frac{(H^+)_p}{(H^+)_c} = 1 - \frac{(Hb')_c}{2(Cl' + HCO_3')_p}$$

(The use of the parenthesis is to indicate concentration of ions.)

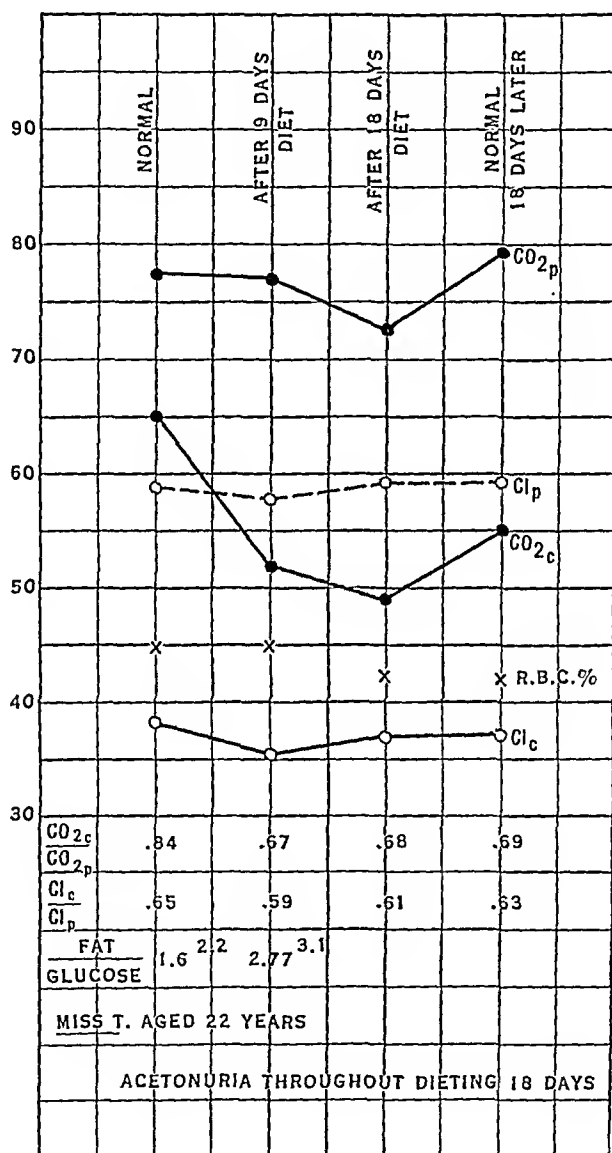


FIG. 3

FIGS. 1, 2 AND 3.—Abscissæ represent c.gm. NaCl and cc. of CO₂ per 100 cc. of plasma or red cells.

In actual practice this law, though not absolutely true, is near enough for our purposes. Its mechanism is well illustrated by one of our experiments (Fig. 4), in which the hydrogen-ion concentration

of a sample of blood has been raised by the addition of hydrochloric acid. It will be noted that the curves representing carbon dioxide combining power (bicarbonate) of both plasma and cells not only fall but converge as more acid is added. The plasma and cell chlorid curves also converge. Convergence of curves means that the ratios $\frac{(\text{Cl}')_c}{(\text{Cl}')_p}$ and $\frac{(\text{HCO}_3')_c}{(\text{HCO}_3')_p}$ rise in value as the blood becomes more acid. Conversely a divergence of curves indicates a more alkaline condition of the blood. Note also that the red cell volume also rises with acidemia; conversely it falls in alkalemia.

Coming now to a consideration of Figs. 1, 2 and 3, we find that in all the bicarbonate reserve of the plasma fell, as was found in the case of children by Weymuller and Schloss.¹¹ But this fall in alkali reserve does not necessarily indicate an acidemia. In Fig. 1 the early convergence of the carbon dioxide curves and of the chlorid curves does, indeed, indicate an acidemia, but the even greater divergence in the second period shows an alkalemia, and in Figs. 2 and 3 there was alkalemia all through the period of the ketogenic diet. Unfortunately the subjects of Figs. 2 and 3 were menstruating at the time of the second blood examination and we are unable to state how far our results have been affected by this fact. Close and Osman,¹ however, have shown that the only effect of menstruation is a slight decrease in plasma carbon dioxide and a slight increase in plasma chlorid. At the time of the third blood examination menstruation had ceased 8 or 9 days previously, and still a condition of relative alkalemia was present. The fall in red cell volume throughout the period of examination can hardly be due to alkalemia, since the most marked fall in cell volume occurs at the end, when the subjects had returned to normal diets. A more plausible explanation is that the repeated losses of blood has caused a slight anemia.

Discussion. In this wholly unexpected alkalemia—accompanied, as is well known, by a further hydration of the body tissues—we have, probably, the explanation of the failure of the ketogenic diet in many cases of adult asthma and epilepsy, though in children the results appear to be much better.

The explanation of the production of the alkalemia is a more difficult problem. We would, however, tentatively suggest that the clue may be found in the work of Hurlley and Trevan,³ who showed that certain ketone derivatives not only produce coma, but also specifically stimulate the respiratory center, producing hyperpnea and increased rate of respiration. This action is due to the unsaturated linkage in the group $-\text{C.OH}=\text{CH}-$ found in these substances, and occurs when the substances are neutral bodies or have been neutralized, so that the effect is not due to an alteration of hydrogen-ion concentration.

The ketonic acids, of course, tend to produce acidemia by combining with the sodium bicarbonate of the blood and raising the

$\frac{(\text{HCO}_3)_c}{(\text{HCO}_3)_p}$ ratio, in the same way as does hydrochloric acid in Fig. 4. But the hyperpnea produced by direct stimulation of the respiratory center by the $-\text{C.OH}=\text{CH}-$ bodies causes carbon dioxid to be blown off in excess by the lungs, leaving a relative excess of uncom-

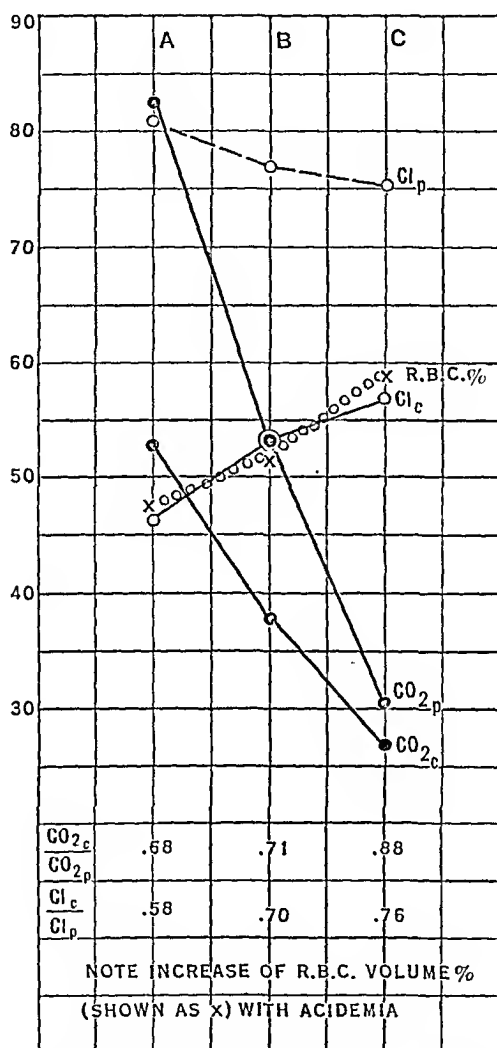


FIG. 4.—Graph illustrating the redistribution of Cl and CO_2 between plasma and red cells when the H content, but not the Cl content, is altered in blood *in vitro*.

In A, 40 cc. of blood + 1.5 cc. 0.5 N NaCl solution.

In B, 40 cc. of blood + 0.75 cc. 0.5 N NaCl solution.

+ 0.75 cc. 0.5 N HCl solution.

In C, 40 cc. of blood + 1.5 cc. 0.5 N HCl solution.

Abscissæ represent c.gm. NaCl and cc. of CO_2 per 100 cc. of plasma or red cells.

pensated bicarbonate in the blood, *i. e.*, an alkalemia. Of course, the kidney tends to restore the $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ ratio in the blood by excreting the excess NaHCO_3 , but as these compensating mechanisms never quite succeed in restoring the ratio to normal (since if they did so

the stimulus to compensate would disappear) the result is that a slight alkalemia remains.

We have then two effects, one tending towards an acidemia, the other tending in the reverse direction. The final result would appear to depend upon which of these preponderates, or the relative proportions in which ketonic acids and —C.OH=CH— groupings are produced.

Conclusions. 1. The ketogenic diet is believed by many to produce an acidemia which is said to have good results in many cases of epilepsy and asthma by combating the alkalemia often associated with these conditions, and causing some dehydration of body tissues.

2. A study of the blood changes produced by the ketogenic diet in 3 normal individuals showed that alkalemia was almost constantly present, accompanied by a fall in both plasma and red cell carbon dioxide.

3. We suggest that the alkalemia is the result of hyperpnea produced by direct stimulation of the respiratory center by certain ketone derivatives in the blood, and that in our experiments this effect outweighed any acidemia produced by ketonic acids, and, further, that the failure of the ketogenic treatment of many cases of epilepsy and asthma is due to the relative preponderance of the former effect.

4. We would further suggest that a study of any conditions tending to raise the ketonic acid:acetone ratio would be of benefit in the treatment of epilepsy and asthma.

NOTE.—To Miss Mabel Flanley, B. S., consulting dietitian of Seattle, Washington, are due our thanks for her great help in arranging and directing the dietetic treatment of our subjects, and to the latter for volunteering their services. Without their valuable help this work could not have been carried out.

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THE COLON CHANGES IN CHRONIC ARTHRITIS COMPARED WITH OTHER CHRONIC DISEASES.*

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RECENTLY the concept has been put forth that in chronic arthritides the bowel may take on a certain configuration, such as redundancy, atony, lack of haustral markings and ileocecal valve incompetency (Pemberton and Peirce,¹ Fletcher and Graham²). In addition, Pemberton has stressed the effect of a low calorie diet, with a minimum carbohydrate fraction, as being particularly beneficial to arthritic patients.

Having had occasion to study a number of arthritides in this dispensary from various angles, we aim here to compare the appearance of the bowel in chronic arthritis and in a group of dispensary patients with various other chronic ailments. This should determine whether the changes were characteristic of chronic arthritis or were merely such as would be found in the bowels of chronic patients subject to the same environmental factors.

Everyone admits that the bowel has changed through the ages in conformity to the type of diet ingested. If it were possible to compare the digestive tract of *Pithecanthropus Erectus* with the digestive tract of the individual of today changes would doubtless be noted. The preponderance of vegetables and fruit, with an excess of roughage eaten for hundreds of thousands of years before the cooking era, certainly made the digestive tract of that era somewhat different from ours. These changes are in a measure comparable to those found in the skull and other osseous development of the ape man of Java, compared with the human skeleton today. In addition to these adaptations of the alimentary tract in response to food and environment, changes in the bowel developed—"as a result, either of congenital anomaly of the colon or of an instability of its autonomic control or from an interplay of both factors" (Kantor³).

The bowel has an intimate relationship both to disease and health. Here is one of the main sources of elimination of the waste products of digestion. Any breakdown in the metabolism of the individual, any impairment in the function of the liver as a detoxifying agent, any curtailment of the excretory power of the genito-urinary tract, any change in the secretion of the digestive enzymes of the stomach

* This investigation was pursued with kind permission of Dr. E. C. Reifstein, Professor of Medicine and Chief of Service.

and upper intestinal tract; the adoption of dietetic fads and fancies, or the inadequate diets now eaten by a large majority of dispensary patients because of economic reasons, show their effect in one way or another on the large bowel. To this number, as a result of our studies detailed below, we must add a group of patients who, like the chronic arthritides, have certain characteristic changes in their bowel. We maintain that this is not typical or peculiarly characteristic of these special diseases, but is more or less a manifestation of chronic ill-health, malnutrition and inadequate diet in general.

Bouchard⁴ and Metchnikoff⁵ stress the importance of intestinal toxemia to disease in general and the prevention of bowel stasis in prolonging life. Lane⁶ and Goldthwait have called our attention to anatomic changes in the intestinal tract, such as bands, kinks and visceroptosis and their effect on intestinal stasis with its resultant toxemia and general ill-health.

All kinds of operations have been suggested to correct the malposition of the colon, the removal of kinks, the resection of parts of the bowel in cases of redundancies. Ileocecal valve incompetencies have also been subjected to operative interference. All these measures have been attended with varying indifferent results.

Pemberton and Fletcher have claimed that in their particular studies, with the improvement in the general arthritic condition, redundancies of the bowel have been lessened, ileocecal valve incompetencies were reduced to a minimum, atony improved and haustral markings were made to appear again where once they were lacking.

In our study we observed very carefully roentgenologically, by means of barium enemas, 25 chronic arthritic cases and 25 cases representative of the average run of dispensary patients coming to the clinic for consultation.

The Roentgen appearance of the bowels of the arthritic patients showed an unusual percentage of redundancies, lack of haustral markings, atonies and ileocecal valve incompetencies. In this respect our results were comparable in every way, with the studies previously made by Pemberton and Fletcher.

We found in our studies that 80 per cent of our arthritic patients showed ileocecal valve incompetency of varying degrees. There was lack of haustral markings exhibited in 64 per cent of our cases. For the most part, these markings were observed in the descending colon. In 40 per cent of our cases atony was exhibited. We found the rather high proportion of redundancies of parts of the colon in 85 per cent of our cases. These redundancies took on various forms, such as plicae, loops and knots.

In the same type of investigation made of our control group we found reduplications in 80 per cent; lack of haustral markings in 78 per cent; ileocecal valve incompetencies in only 16 per cent; atony of the bowel in 8 per cent. It will be seen that the chief point of difference between the two groups is in the higher incidence



FIG. 3.—Mr. P. R. Chronic arthritis. Ileocecal valve incompetency.



FIG. 2.—Mr. N. H. Chronic arthritis. Redundancy.

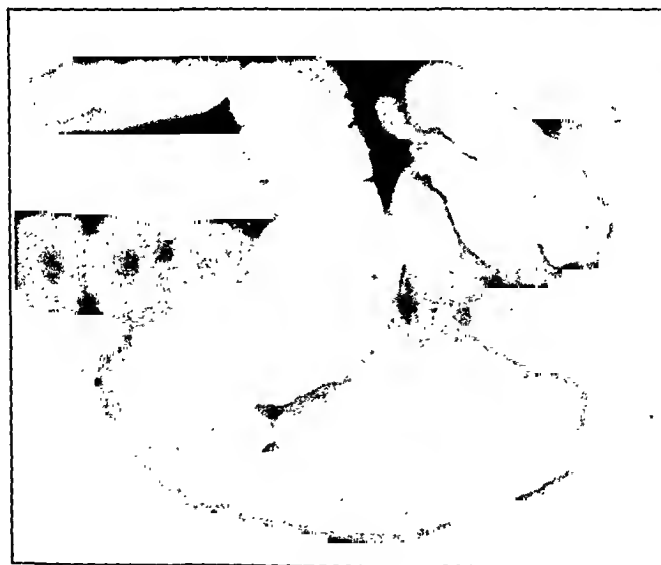


FIG. 1.—Mrs. V. H. Psychoneurosis, anxiety state. Redundancy.



Fig. 4.—Mrs. H. D. Psychoneurosis, anxiety state, metrorrhagia. Lack of haustral markings. Redundancy.



Fig. 5.—Mrs. A. M. Pulmonary tuberculosis (arrested); rheumatic heart disease; ptosis and redundancy.

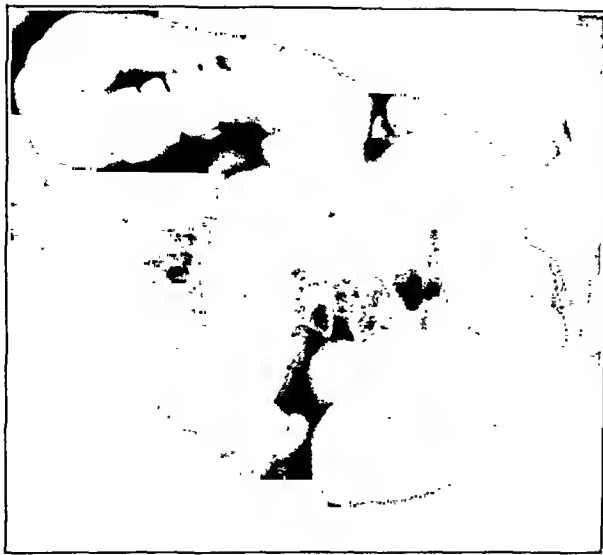


Fig. 6.—Mr. E. F. Chronic arthritis. Ptosis and redundancy.

of ileocecal valve incompetencies exhibited in the chronic arthritides. The etiologic significance of this finding in relationship to arthritis will not be discussed in this paper.

Redundant Colon. A redundant colon is one of the most commonly seen departures from the normal colon. The ideal colon would supposedly take almost a straight path in each of its divisions from the cecum to the rectum. The redundant colon, as its name suggests, has its length much increased by kinks, pleats, twists or loops. The normal incidence of redundancies found by Curschmann⁷ was 6 per cent; Kantor⁸ found an incidence of 9.2 per cent; in a later series he changed this percentage to 19 per cent; Bryant,⁹ working with postmortems, found 14 per cent of redundancies of the colon.

The redundancies of the colon most often occur in the pelvis. The normal colon is about 1.5 m. in length. The average colon is able to hold a little over 1 quart of fluid whereas the redundant colon is able to retain much more than that amount, even up to 3 quarts. The significance of redundancy of the colon is a matter of conjecture. It is fair to presume that there must be a large number of patients who have redundancy with absolutely no symptoms, just as it is in the case of a large number of asthenic individuals with ptosis who complain of no symptoms. They probably are more prone to volvulus and constipation than are people with normal colons.

Examples of redundancies can be seen in Figs. 1 and 2.

Ileocecal Valve Incompetency. The ileocecal valve is formed by the invagination of the ileum into the cecum. It has a definite sphincter control, formed by the circular muscle fibers; the longitudinal muscle fibers have been lost. The efficacy of the valve is obtained in the oblique manner in which the ileum enters the cecum, almost in the same manner as the ureter enters the bladder.

The competency of this valve has been a question which has engaged the attention of investigators for a great number of years. The significance of incompetency is still debatable. It certainly is met with in normal individuals in a small percentage of cases and any pathologic significance attributed to this isolated phenomenon alone is speculative rather than based upon scientific corroboration. Keith,¹⁰ Hurst,¹¹ Case,¹² Sticlin¹³ and Jones¹⁴ are only a few of the men who have given this matter serious attention. It was Cole¹⁵ who first recorded this phenomenon roentgenologically in 1902 and since then it is seen rather commonly in Roentgen ray studies of the bowel with contrast material.

Fig. 3 is an example of ileocecal valve incompetency. Figs. 1 and 2 show a competent ileocecal valve.

Lack of Haustral Markings. Normally, there are 3 haustra in the colon; the upper, the middle and the inferior haustrum. Of these, it is only possible to see 2. The third haustrum is hidden by the central axis of the colon. Haustration is caused by the

circular fibers which, acting with a tænia, produce the usual picture of haustration as seen in the roentgenograph. In certain conditions, as in mucous colitis, there may be loss of these haustrations which varies from a small degree to complete absence. In certain extreme cases there are only very small indentations in the lumen of the bowel. This is also seen in the group of chronic cases studied above, without any evidence of colitis.

Fig. 4 shows lack of haustral markings, together with marked redundancy of the left bowel.

Ptois. Ptois or coloptosis means dropping of the colon, and may be either congenital or acquired. Asthenic individuals are more apt to acquire it than any other type. It is found much more frequently in women than in men and about 20 per cent of all women have it. Any chronic wasting disease with resulting malnutrition may cause a loss of power of the supporting structures of the intestines and so produce ptois. However, it most intimately concerns itself with loss of muscle tone in asthenic, congenital, constitutional states. Ptois of the bowel further depends to a considerable degree on the amount of space in the abdominal cavity, the position of the diaphragm and the liver and the amount of fat deposited in the roots of the mesentery of the intestines.

When the drainage of the colon is retarded in cases of coloptosis symptoms may arise as a result of fermentation and putrefaction of its contents, but in most cases it is fair to state that no symptoms referable to ptois of the bowel exist. The majority of such patients have no symptoms referable to this condition unless complicated by other factors.

Examples of ptois are illustrated in Figs. 5 and 6.

It is our opinion that any isolated one of these variations described above may be seen in individuals without causing any particular symptoms, but they may assume a real significance when associated with a chronic wasting disease or may be an expression of chronic disability itself.

We believe that a study of any large group of chronically ill patients would disclose similar variations in the bowel from the normal. With improvement in the general wellbeing of these patients, due to a better dietary régime, more ideal living conditions and freedom from the stress and strain of economic requirements, a more normal bowel would be seen.

Summary. A study of the bowel of 25 chronic arthritic cases shows a high percentage of ileocecal valve incompetencies, reduplications, lack of haustral markings and atonics.

A similar bowel study of 25 dispensary patients with nonarthritic chronic ailments reveals also a high incidence of the above variations.

There is a greater percentage of ileocecal valve incompetency in the arthritics than in the controls, the significance of which we do not attempt to explain at this time.

It is suggested that the expression of the abnormalities in the bowels of the arthritics, as well as in the control cases, is a manifestation of chronic diseased states rather than a condition which is peculiar to the chronic arthritides.

NOTE.—The material for this study was furnished and collected by Dr. Albert A. Bailey, resident physician, Syracuse Free Dispensary.

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INSULIN RESISTANCE DUE TO ALLERGY.

WITH REPORT OF A CASE.*

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ALLERGIC phenomena occurring in cases in which insulin is used are manifested in a variety of ways, as was shown in a review of insulin allergy recently published.² The majority of allergic reactions are characterized by local irritation at the site of injection, which is of no serious consequence and merely causes annoyance. Sometimes there is a severe local reaction which causes intense distress, so that further treatment may become difficult. Rarely

* Submitted for publication October 5, 1932.

there is a generalized anaphylactic reaction in which occur urticaria, nausea, vomiting and occasionally circulatory collapse.

The incidence of allergic reactions to insulin is variable. In cases treated at The Mayo Clinic in 1930 and in the early part of 1931 there was some sort of reaction in 1 of every 7 or 8 cases. The number of reactions encountered previously was smaller and the number has also declined recently. In Table 1 are shown the data previously reported, with later figures added. The cause of these changes cannot be explained satisfactorily. Reactions occur from insulin obtained from every source. They occur from insulin made by every manufacturer and from extracts of pancreas of various species. There are, however, differences in the number of reactions encountered with different lots of insulin. One must, therefore, suspect that variability in these reactions may be due partly, at least, to differences in the quality of the preparation. They may perhaps become less common as a result of the efforts which are being made constantly by the manufacturers to improve their methods of extraction and purification. It cannot be expected, however, that allergic phenomena will disappear entirely, for certain subjects show hypersensitiveness to insulin of absolute purity which has been prepared in crystalline form.

TABLE 1.—INCIDENCE OF ALLERGIC REACTIONS.

Date.	Patients treated.	Reactions.	Per cent.
1927—First 6 months	192	7	3.9
Second 6 months	236	7	2.9
1928—First 6 months	168	6	3.5
Second 6 months	211	11	5.2
1929—First 6 months	183	12	6.5
Second 6 months	177	17	9.6
1930—First 6 months	216	34	15.7
Second 6 months	185	23	12.4
1931—First 6 months	206	29	14.1
Second 6 months	202	19	9.3
1932—First 6 months	132	9	6.8

In the majority of cases desensitization occurs spontaneously as the treatment with insulin is continued, and if the irritation is slight it may give no concern. In fact, the patient often fails to bring it to the notice of the physician. Yet attention to these cases, which are so often overlooked, may give gratifying relief. When there is a severe inflammatory reaction at the site of the injection, or when general anaphylactic phenomena appear, something must be done. The results in 100 consecutive cases of insulin allergy considered¹ elsewhere² are summarized here. In 8 cases spontaneous desensitization occurred during regular treatment. In 64 cases there was relief from the irritation following use of insulin from a different source, either insulin made by a different manufacturer, or made by the same manufacturer from the pancreas of a

different species.* In most of these cases spontaneous desensitization might have occurred eventually if nothing had been done, but the early relief given by changing the kind of insulin was significant. In 6 cases irritation from the injections continued, but was not serious enough to interfere with treatment. In 22 cases in which insulin was used only temporarily hypersensitiveness persisted.

Efforts to bring about desensitization deliberately have not been very satisfactory, but in 1 case of the last group, temporary desensitization to deal with an emergency was successful. A middle-aged woman who had had mild diabetes for 7 years required insulin temporarily on 3 occasions. When used first, after a pelvic operation, there was a local reaction. On the second occasion, when given at the time of treatment of varicose veins, there was an urticarial eruption accompanied by prostration for 3 days. It was needed again after an operation for empyema of the gall bladder, which caused such serious aggravation of diabetes that acidosis developed. An attempt at that time to administer ordinary insulin caused a general reaction with alarming symptoms. A solution of crystalline insulin, obtained from Dr. D. A. Scott, of Toronto, caused only a mild local reaction. It was administered in minute dosage at the beginning, the injections being repeated at short intervals and gradually increased. This resulted in desensitization, so that within 24 hours effective doses could be tolerated. The patient was thus rescued from threatening coma.

In none of the cases reported in a previous paper was there any interference with the effect of insulin on diabetes. Glycosuria and hyperglycemia were controlled with a dosage within the usual limits. However, in the recent case reported herewith there was unusual resistance to its action. Diabetes relatively refractory to insulin has been encountered with hemochromatosis¹ and under certain other conditions, but is extremely rare. We have been able to find records of only 4 cases in which resistance to insulin seemed to occur as a result of allergy, or in which this was considered as a possible explanation. One case was reported by Williams. Acidosis was present and continued until the kind of insulin used was changed. Karr, Kreidler, Scull and Petty had a patient who was given several hundred units daily for a long period without complete control of symptoms. The occurrence of skin reactions from the injections of insulin led to serologic tests, and the patient was treated with serum from a rabbit to which the patient's serum had been administered. Subsequently an abrupt change occurred so that diabetes became latent without treatment. Rudy reported the occurrence of diabetic

* Insulin specially made from the pancreas of sheep was supplied by E. R. Squibb and Sons through the courtesy of Dr. John F. Anderson. It was used in our investigation but did not prove to have practical value, since patients sensitive to commercial insulin from pancreas of hogs and cattle were sensitive to this. Eli Lilly Company also supplied special preparations of insulin for trial.

acidosis temporarily resistant to insulin in a case of urticaria. The fourth patient, Foerster's, had urticaria attributed to sensitiveness to insulin, also mild acidosis. Large doses of insulin were given without apparent benefit; in fact, the condition improved when the insulin was stopped although glycosuria continued.

Report of Case.—A woman, aged 55 years, was found to have mild diabetes in March, 1921. She neglected treatment until acidosis occurred in 1924. Insulin was then used temporarily and treatment with "neosynthalin" was later tried intermittently, but, as a rule, dependence was placed on dietary treatment alone. The patient usually had good health, although the urine frequently contained a small amount of sugar. When she came to The Mayo Clinic, April 6, 1932, the submaxillary lymph nodes were enlarged. This had appeared several weeks previously, when she was ill with a severe respiratory infection. The diabetes had been aggravated at the same time and glycosuria had continued so that treatment with insulin was begun in a dosage of 15 to 20 units daily. About 10 days later a mild local allergic reaction developed.

When the patient was first seen at the clinic she stated that the submaxillary swelling was subsiding, but 3 weeks later it appeared to be larger. A gland was removed from the neck, under local anesthesia, April 30, 1932. This was diagnosed lymphosarcoma, Hodgkin's type.

On the afternoon of April 30 the patient became seriously ill. In the evening she vomited repeatedly. Later marked prostration, difficulty in breathing and drowsiness developed. When she was seen at her home at 9 p.m. she was on the verge of coma, but was able to sit up in bed and answer questions. She was given 40 units of insulin at once and transferred to the hospital. More insulin was given, but the condition became gradually worse, and soon there was complete loss of consciousness. The carbon dioxide combining power of the plasma fell to 6 per cent by volume. The heart began to fail and the systolic blood pressure dropped to 80 mm. There was a sudden change in the heart action 4 hours after admission, and it was difficult to feel the radial pulse. Auricular fibrillation followed later. Injections of insulin were repeated at intervals, with the dosage increased. In 12 hours the patient had received 500 units with only slight response. The blood sugar remained high, and the carbon dioxide combining power of the plasma was extremely low. Sodium bicarbonate was administered once by proctoclysis and three times intravenously with benefit. The labored breathing became easier and the circulation improved. The patient opened her eyes and was able to take a drink, yet her condition remained critical.

About 12 hours after admission to hospital a diffuse urticarial eruption, with numerous large blebs, appeared over the patient's entire body. The possibility that the resistance to insulin was due to allergy was recognized. The kind of insulin used was altered, and a solution of crystalline insulin was then employed. One hundred and fifty units were given intravenously at once, followed by small doses at short intervals. There was an immediate change and the ketosis was soon overcome. The carbon dioxide combining power of the plasma, elevated somewhat by the treatment with soda, now rose to normal. The blood sugar was continuously elevated by injections of glucose solution given at intervals.

The patient seemed out of danger from diabetes, but the cardiac condition was serious. Profound prostration continued; the blood pressure was low; fibrillation was noted intermittently. Since the supply of crystalline insulin was limited, an effort was made to use commercial insulin. It was diluted and used in minute doses to begin with, the size of the dose being increased gradually. Some inflammatory reaction occurred at the site of

each injection. The carbon dioxide combining power of the plasma remained normal, but because of precautions to avoid hypoglycemia, which might affect the heart unfavorably, the blood sugar was permitted to remain high. The heart continued to fail and 4 days after admission death occurred. Toward the end even more caution was used in giving insulin. A blood test made 10 minutes before death showed that the blood sugar had risen to 500 mg. for each 100 cc. and the carbon dioxide combining power of the plasma had fallen to 36 per cent by volume. More insulin should have been given before this, but it would not have affected the outcome, since the patient was then moribund (Table 2).

TABLE 2.—DATA ON CASE REPORTED.

Date.	Insulin units.*	Time.	Blood sugar, mg. for each 100 cc.	Carbon dioxide combining power, per cent.
April 30 . . .	160 A	9.30 P.M.	536	19.2
		12.00	462	6.0
May 1† . . .	340 A	1.00 A.M.	448	6.0
	178 T	2.00 A.M.	448	6.0
		3.30 A.M.	390	6.0
		5.30 A.M.	462	13.6
		7.15 A.M.	429	12.0
		9.30 A.M.	517	13.6
		10.30 A.M.	517	36.2
		12.30 P.M.	502	40.0
		3.00 P.M.	508	50.4
		5.00 P.M.	476	54.1
		7.30 P.M.	423	50.4
		10.30 P.M.	385	54.1
Total . . .	518			
May 2 . . .	156 T	7.10 A.M.	370	56.0
	30 B	11.00 A.M.	429	60.5
		2.00 P.M.	429	48.5
		7.15 P.M.	400	54.1
		10.30 P.M.	361	54.1
Total . . .	186			
May 3 . . .	64 T	8.00 A.M.	300	
	48 C	12.15 P.M.	353	
		4.30 P.M.	429	
		9.30 P.M.	435	
Total . . .	112			
May 4 . . .	8 C	6.30 A.M.	500	36.2

* A, B and C varieties of commercial insulin; T, crystalline insulin.

† Three hundred cubic centimeters 5 per cent sodium bicarbonate solution given by continuous proctoclysis during the night; 400 cc. given intravenously at 12.30 A.M.; 500 cc. given intravenously at 9.30 A.M.

The postmortem examination disclosed an advanced degree of coronary sclerosis, with rather marked narrowing of all branches of the coronary arteries near their orifices. The muscle of the left ventricle revealed acute infarction, the infarcted portion extending into the septum and involving portions of the papillary muscles posteriorly. Approximately a third of the substance of the muscle was affected. Microscopically this infarcted zone was revealed as a region of necrosis with a margin of polymorphonuclear leukocytes and hemorrhage. Older fibrous foci were also present.

The gall bladder contained a large, single calculus, which completely filled the lumen. The wall of the gall bladder was thickened and increased in density. Surrounding this wall there was edema of the tissues, with beginning purulent infiltration. Examination of the neck failed to reveal any lymph nodes with involvement typical of Hodgkin's disease, but re-

examination of the lymph node removed 4 days before death confirmed the impression of a Hodgkin sarcoma. In the lungs there was bronchopneumonia, with beginning pleuritis in the dependent portions of both lower lobes. Occasional foci of fat necrosis were seen in the pancreatic fat.

Further minor details consisted of fine points of hemorrhage in the skin over various portions of the body, chronic tuberculosis of the hilus nodes of the lung, and advanced melanosis of the colon. Microscopic examination of the pancreas revealed only minor changes in the islands, which might point to degenerative conditions consistent with diabetes.

The factor immediately responsible for death was the cardiac infarction.

Comment. The sudden development of diabetic coma in a case in which treatment previously had been successful, and the lack of response to huge doses of insulin, were obviously the result of interference with the action of the insulin administered. The existence of hypersensitiveness toward insulin, manifested by local irritation at the site of injection, and later by the appearance of urticaria and cutaneous blebs, points to an allergic phenomenon as the cause.

It is so rare for allergy to cause resistance to insulin that there are no rules to guide treatment under such circumstances. Five modes of procedure have been applied in this and other cases in which the problem has arisen: (1) Stop treatment with insulin, in the hope that spontaneous adjustment will take place. This may be attempted with a patient free from ketosis, or with ketosis of mild degree, as in Foerster's case, but would be foolhardy in the presence of threatening coma. (2) Increase the dosage of insulin to the point where it does become effective, as was done in Rudy's case. (3) Change the kind of insulin, as did Williams, using preferably solution of crystalline insulin in the hope that it may be tolerated. (4) Attempt desensitization, choosing the kind of insulin, if any, which is best tolerated, giving it in minimal doses at the beginning of treatment, then gradually increasing to effective doses as tolerated. (5) Endeavor to prepare a serum which will overcome the disturbance, as was claimed by Karr, Kreidler, Seull and Petty. In the case reported here, treatment was attempted by a combination of the third and fourth plans. The patient began to respond to the treatment, and might have recovered had it not been for the serious injury to the heart, which occurred when the acidosis was at its peak.

The infarction of the heart may be explained as a result of the abnormal lowering of the blood pressure, which resulted from the intense acidosis. The patient had sclerotic coronary arteries, and the high blood pressure usually present presumably maintained adequate flow through them. When the blood pressure fell the flow must have become sluggish so that thrombosis could readily occur.

The lymphosarcoma was another factor which would have affected the ultimate prognosis. Also, the biopsy complicated the situation. Diabetes is sometimes aggravated by even simple surgical pro-

cedures. Yet the extreme resistance to treatment manifested by the development of coma which was refractory to commercial insulin is attributed to the allergic phenomenon.

Summary. Allergic reactions to insulin have become less frequent but still occur in a significant number of cases. Serious symptoms are uncommon, and alteration of the action of insulin has seldom been encountered.

A report is given of a case of diabetes which became refractory to insulin because of allergy. Coma developed and at first could not be overcome with massive doses of commercial insulin. Treatment with solution of crystalline insulin brought about partial recovery, but death occurred four days later from cardiac infarction.

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ALLERGIC MIGRAINE.

II. ANALYSIS OF A FOLLOW-UP AFTER FIVE YEARS.*

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In 1927 the author reported¹ 33 cases of migraine, 36 per cent of whom were relieved following the discovery and avoidance of allergenic foods. The presence of an allergic factor in many cases has been substantiated by several workers, notably Rowe,² Rowe and Richet,³ Eyermann,¹¹ Balyeat,⁴ and Beecher,⁵ although very recently Coltman⁶ reports that migraine due exclusively to sensitization was not observed in his series, studied from the allergic point of view. The present report is based upon 82 cases, all that the author has studied allergically up to the present. Nineteen were referred for examination only and I have been unable to follow them. The remaining 63 have been adequately followed over periods up to 11 years and form the material for this analysis.

In my analysis 5 years ago I reported 10 cases relieved on specific food avoidance. Five years later, 3 are dead but con-

* Read before the annual meeting of the Michigan State Medical Society at Kalamazoo, Mich., September 15, 1932.

tinued free of migraine until their death (Cases 6, 7, 10); 4 continue symptom free (Cases 2, 3, 4, 5); 2 report return of symptoms. The first (Case 1) has moved to a distance and has not been seen in 5 years. She now reports that the original foods still cause migraine but that she had other attacks of unknown cause. A few months ago she had 3 devitalized teeth extracted and has since been symptom free. The other case with recurrence of symptoms (Case 9) was relieved for 3 years, after which symptoms returned. She is an Armenian, does not speak English well, finds coöperation rather difficult and has had a long period of anxiety over financial reverses which recently culminated in the bankruptcy of her husband. The last of these 10 original cases has not been traced (Case 8). Seven either continue well or continued well until their death. Information is not available on 1 and the remaining 2 have had a return of symptoms which, however, can be at least partially explained.

Results in the present series of 63 are classified as: (a) excellent, (b) good, (c) fair and (d) no relief. *Excellent* means that on the avoidance of specific allergenic foods the patient remains entirely free from headache. *Good* indicates that on avoidance the individual is nearly symptom free but with occasional headaches, usually traceable to some other definite nonspecific cause. *Fair* indicates persistence of headaches in spite of the fact that the individual has demonstrated by trial that the specific foods will cause migraine: a specific allergic factor has been demonstrated, but its removal has not given relief.*

Of the 63 cases, 25 report excellent results, 7 good, 11 fair and 20 no relief. There is evidence of an allergic factor (fair, good and excellent), in 68.3 per cent; satisfactory results were obtained (good and excellent) in 50.8 per cent, and excellent results in 39.7 per cent. Since extraneous factors enter into the fair-result cases, the following analysis of good and poor results will not include the fair cases unless so stated. The good and excellent will be grouped together as "cases relieved," for comparison with "cases not relieved."

Of the 43 showing evidence of an allergic factor (good, fair and excellent), 35 have been followed for more than 1 year since testing, 18 for more than 5 years, 7 over 9 years and 1 for 11 years.

If we may obtain excellent results in 40 per cent, good results in 50 per cent and evidence of an allergic factor in nearly 70 per cent, it seems advisable to attempt an analysis to determine the reason for reported failure to do as well⁶ and particularly in an effort to increase still further our percentage of good results.

Identification. The question might be raised, are we dealing with true migraine? The author has seen a few cases of headache due to

* Variations in the percentages of good results from allergic therapy in migraine recently reported^{7,10} are presumably due to the selection of varying standards as measures of the adequacy of the treatment.

inhalant allergy indistinguishable from migraine, but these are not included. All of those reported have been cases of ingestant allergy. They are typical, hereditary, periodic headaches, often with associated nausea, vomiting and eye symptoms and sometimes influenced by the catamenia, in which refractive errors and other factors have been ruled out or controlled, and in whom the symptom has been present over a period of years. Unilateral distribution of pain, while frequently recorded, or recorded as recurring at times, has not been insisted upon as a requisite for the diagnosis of migraine.

Possibly it might be more appropriate to have designated this series "periodic or recurring sick headache," since hemierania has not been considered a requisite, but the term has been used in its commonly accepted significance as "migraine headache." Moreover, as has been brought out by Rinkel and Balyeat,¹⁰ unilateral localization is not necessarily a constant characteristic of migraine. Furthermore, most of the cases reported did describe unilateral localization at times. The term allergic headache¹¹ is not desirable since this is a designation that can be arrived at only after therapeutic trial and automatically eliminates the cases not relieved. It is a *post-hoc-ergo-propter-hoc* diagnosis.

Clinical Data. *Nausea and Vomiting.* Of the patients, 85.2 per cent complained of nausea and 60.4 per cent of vomiting with their attacks. Only about half of the no-relief cases suffered nausea and vomiting, while 27 of the 32 that were relieved had nausea and about half had vomiting.

Eye Symptoms. Of the entire series of 63, 39.9 per cent had eye symptoms, manifested as follows: Scotoma, 3 cases; blindness, 4; hemianopsia, 1; extraocular palsy, 2; partial blindness, 5; blurring of vision, 2; eye symptoms (type not specified), 2. Seven of 32 relieved cases gave a history of eye symptoms. Eight of 20 not relieved did likewise.

Age of Onset. McClure and Huntsinger⁷ found, in a series of 78 patients, that migraine begins before the age of 20 years in 83 per cent and before the age of 30 in 95 per cent. In this series the symptoms began before the age of 20 in 65 per cent and before the age of 30 in 91 per cent. Considering the relatively small number in both series this shows sufficient correlation for us to state that the age of onset in this series is characteristically that of migraine. (Table 1.)

TABLE 1.—AGE AT ONSET.

[illegible]

Family History of Migraine. Among the 51 in whom the family history was recorded, 38 gave a family history of periodic sick headaches; 83 per cent of the relieved cases and 69 per cent of those not relieved gave a family history of migraine.

Sex. Fifteen were males and 48 females.

Catamenia. Of the 22 females that were relieved, 5 experienced exacerbation with the catamenia. Of the 16 not relieved, 2 gave a similar history.

Duration. The duration of the illness is recorded as from 2 to 55 years. The average duration in those relieved was 21 years, in those not relieved 15 years. Of the entire series the duration was recorded in 52. In 14 it had been less than 10 years; in 38, 10 years or more. Of the 26 who were relieved, 20 had had their migraine 10 years or more, 4 of them having had it for over 45 years. Of the 15 with no relief, 11 had had it for over 10 years.

Periodicity. In 48 of the 63 the periodicity was recorded. In 25 the headaches occurred 2 or more times each month; in 17, at intervals varying around 1 or 2 months; in 6, at longer, irregular intervals such as 2 or 3 times each year.

Allergic History. If migraine is partly or wholly allergic, our experiences would lead us to anticipate a history of other allergic manifestations in the individual and a family allergic history.

Over half, 33, recorded other allergic symptoms as follows: Asthma, 8 times; hay fever, 19; urticaria, 16; eczema, 9. Thirty gave a negative history for other allergic manifestations.

Complete family allergic history was recorded in 51. In 43 of these 51, family allergic manifestations were distributed as follows: Asthma, 12; hay fever, 14; urticaria, 5; eczema, 10; migraine, 38. Only 8 had a negative family history for other allergic symptoms or migraine.

Results. As had been stated, 50.8 per cent were relieved, 39.7 per cent entirely so; 68.3 per cent showed evidence of an allergic factor. The average duration of relief in the 32 relieved cases has been 4.4 years, ranging from several months to 11 years.

Twenty-one replied to the question whether they have found that, after having avoided the causative foods for a period of time, they now find that they can eat them with impunity; 7 (one-third) find that they must continue to avoid them. Two-thirds can eat them at times. The period of avoidance among those who were able to return to these foods ranged from 1 to 9 years. On the other hand, of those who still have symptoms from prohibited foods, 1 has avoided for 10 years, 1 for 6 years, 2 for 5 years and 1 for 4 years. The obvious interpretation is that some appear to lose their sensitizations, while in others it tends to persist indefinitely, certainly as long as 10 years.

Replies such as the following are illustrative of those who find that they can eat the forbidden foods at times: Mrs. B. can eat

all of the forbidden foods except fish and cabbage. With Mrs. F., the foods cause symptoms only when she is fatigued. Miss F., sensitive to wheat, can sometimes eat it as long as from 3 to 5 weeks but eventually develops headaches therefrom. Mr. G. states that wheat or beans eaten at 1 meal will cause no symptoms but will do so if taken for 6 meals straight. Miss O. can eat all forbidden foods in moderation but not in excess.

Analysis of Factors Influencing Results. *Age.* We find that age is not a factor. Four of the relieved patients were over 60, 1 over 70 years. The curves of age distribution are entirely comparable in the relieved group and those not relieved; in both the peak is at ages 30 to 35 years.

Duration. Duration does not appear to be a great factor. The maximum duration in the relieved group is 55 years (2 cases); in those not relieved, 45 years. The average duration is greater in the relieved group (21 years) than in the unrelieved group (15 years).

That age and duration are not factors influencing results is what we would anticipate if migraine were an allergic manifestation. It is to a great extent the case in the other allergies and is what one would expect in view of the fact that the condition is not associated with permanent organic alterations. If the cause can be discovered and removed one would expect return to normal no matter what the duration, provided secondary degenerative changes have not occurred.

Periodicity. One would expect that, the less frequent the attacks, the easier it would be to find the offending cause. This is borne out in limited degree in our analysis. Of those in whom the periodicity was measured in weeks 26 per cent failed to improve. Of those in which it was measured in months 29 per cent failed to improve. Of those having irregular attacks at much longer intervals only 17 per cent failed to improve. With longer intervals between the attacks the cause may be more readily discovered.

Sex. Here we meet with a surprise. Of the females 48 per cent were relieved and of the males 60 per cent. Results were distinctly better among the males. The reason for this is conjectural, but the author would suggest that a chief factor is the greater ease with which a man may adhere to his diet. The woman is constantly subjected to temptation in the kitchen, at card parties and the like, while the man at home must eat what is placed before him. In the restaurant he scans a long menu with his specific prohibitions in mind.

Catamenia. Of 7 women having headaches with the catamenia, 5 were relieved and 2 were not relieved. The catamenia acts only as a nonspecific exciting factor in allergically predisposed individuals; if the allergy is controlled the pelvic state will not interfere with good results.

Constipation. The same remarks apply to this factor. Twenty-five stated definitely that they were chronically constipated. Of these 13 were relieved, 4 had fair results and 7 were not relieved. No material change was made from the patient's previous method of controlling his constipation.

Blood Pressure. Systolic blood pressure in relieved cases ranged from 100 to 192; in those not relieved, from 90 to 200. Of 23 relieved cases only 3 had blood pressures below 110 and only 5 were above 145. The blood pressure range was such as is usually observed in office routine.

Chief Complaint. Some patients came for study primarily because of the migraine. Others came for different reasons and mentioned their sick headaches incidentally. The percentage relieved was the same in both groups.

Inheritance. Of 29 with a family allergic history or family history of migraine 51.7 per cent were relieved. Of 9 without family allergic history only 33.3 per cent were relieved. This limited evidence suggests that the stronger the family history of allergy or migraine, the more likely are we to find an allergic factor, thereby obtaining relief.

Other Allergic Manifestations. Of 24 without other allergic manifestations 37.5 per cent were relieved; of 21 showing other allergic manifestations 62 per cent were relieved. Here again the inference is that confirmatory evidence of an allergic state increases the probability of good results.

Gastrointestinal Complications. The information available on this question is not sufficiently detailed to be of great value. Gastrointestinal studies were limited to history and physical examination with occasional gastric analysis, biliary drainage or Roentgen ray studies. Since these were not routine no statistical analysis can be attempted. In 2 a diagnosis of visceroptosis was made. One obtained relief, the other no relief. Four suffered from a complicating colitis, 2 obtained relief and 2 none; 4 had gall bladder disease, of whom 1 was not relieved, 1 obtained fair results and 2 were relieved without surgery.

Nonallergic Factors. In Table 2, Column 1, we find listed, by number of times mentioned, the reason given by good-result cases for some persistence of their headache. In Columns 2 and 3 the same is recorded for the fair-result cases; Column 2 being the reasons assigned by patients, and Column 3 the explanation reached independently by myself prior to receiving their reports. Columns 4 and 5 provide the same information on those who obtained no relief. While some of these factors are more difficult to control than others, it is at once obvious that the more completely they can all be rectified, the better will be the ultimate results.

Character of the Skin Reactions. The interpretation of the skin reaction is probably the most important factor in obtaining results.

The author has emphasized elsewhere⁸ the importance of attaching possible significance to the borderline reaction and to the delayed positive. Had these types of reaction been ignored in this series the results would have been far inferior.

TABLE 2.—NONALLERGIC FACTORS.

Reasons given for attacks.	In 7 good- result cases.	In 11 fair cases.		In 20 cases not relieved.	
		By author.	By patient.	By author.	By patient.
Unknown	4	1	11	3
Fatigue	5	8
Worry	1	1	1	..	4
Excitement	2	..	2	..	1
Nervousness	2	2
Constipation	3	..	3	..	3
Catamenia	1	..	1
Strong light	1	1
Sleeplessness	1
Hunger	1
Exertion	1
Eyestrain	2	1	1
Thyroid deficiency	1	1
Noncoöperation	2	..	7	..
Colitis	1	..	1	..
Cholecystitis	1	..	1	..
Tuberculosis	1
Purpura	1
Dust	1
Tooth infection	1

In 28 relieved cases the immediate skin reactions to the offending foods were positive in 10, being strongly positive in but 5. In 9 they were borderline, in 5 barely suggestive and in 4 the immediate reactions were negative. The immediate reactions were definitely positive in only a little over one-third.

The delayed reactions were read after 6 and 24 hours. In 3 of the 28 (10.5 per cent) the delayed reactions alone were positive, the immediate reactions having been negative. In 6 (21.4 per cent) the delayed reactions were the only definite positive ones, although the immediate reactions had been borderline or suggestive. In 10 (35.7 per cent) none of the 3 readings, the immediate or the 2 delayed, was stronger than borderline.

Roughly, therefore, of those who were relieved, about one-third gave positive immediate reactions, one-third positive delayed reactions of diagnostic significance, and one-third gave no stronger than borderline reactions throughout, which, however, were of diagnostic significance.

It is of special interest to note that among 18 who were not relieved, 8 or nearly half also gave positive reactions, 2 of which were strongly positive. One is tempted to conclude from this that even with those who received no relief from allergic therapy, allergy is probably actually playing a part.

Foods Responsible for Migraine. It is by now a matter of common experience that one may react positively by skin test to an allergen which will nevertheless not produce symptoms. In each case with the onset of treatment the patient was given a list of the positive and borderline reacting foods. One would expect that the patient would find that some of these foods produced symptoms while others did not. This would be especially true with the borderline reactions. Table 3, Column 1, lists the foods which the patient was advised to avoid. Column 2 lists those foods which the patient subsequently reported as actually causing migraine. This second listing is decidedly reduced. In all, 293 foods were listed for the patients on the basis of the skin reaction, and of these 140 were found responsible for symptoms.

TABLE 3.—FOODS CAUSING MIGRAINE.

	Positive reactors.	Caused trouble.	Discovered by patients, times mentioned.
Wheat	19	19	
Rye	1	1	
Barley	1	1	
Oat	3		
Rice	2	1	1
Corn	4	2	
Cocoanut	1	1	
Pineapple	1		
Onion	6	4	2
Asparagus	5	2	
Banana	10	5	
Ginger	7	1	1
Fig	1		
Buckwheat	1	1	
Walnut	2		
Pecan	3		
Spinach	4	1	
Beet	4		
Turnip	7	2	2
Cabbage	6	2	
Cauliflower	4	1	
Kohlrabi	1	1	
Brussels sprouts	1	1	
Mustard	2		
Raspberry	2	1	1
Strawberry	4	2	1
Apple	6	3	1
Pear	6	1	
Almond	3	1	
Prune	2		
Cherry	4		
Apricot	2	1	
Peach	5	1	2
Pea	13	8	
Kidney bean			
Peanut	13	9	
Blackeye pea			
Lima bean			
Bean	13	7	
Lemon	2	..	2
Grapefruit	3	..	1

	Positive reactors.	Caused trouble.	Discovered by patients, times mentioned.
Orange	4	1	1
Grape			
Cottonseed	1	1	
Okra			
Cocoa	12	8	
Tea	5	1	
Celery	10	2	
Carrot	10	1	
Sweet potato	4	2	1
Tomato	5	2	
Peppers	2	1	
Eggplant	1	1	
Potato	3	1	
Coffee	3	2	
Squash	6	1	
Cantaloupe	5	2	1
Watermelon	1	1	1
Cucumber	1		
Lettuce	6	4	
<i>Animal Foods:</i>			
Beef	1	1	
Veal	2		
Milk	9	9	1
Cheese	1	2	2
Egg	9	4	1
Chicken			
Pork	6	6	2
Lamb	4	2	
<i>Sea Foods:</i>			
Crab	1
Oyster	2	1	
Fish	2	2	
Sardine	1
Salmon	1
Tuna	1	1	
Shad	1	1	
<i>Miscellaneous:</i>			
Whisky	2
Acid foods	1
Chicken liver	1
Ice cream	2
Sweetbread	1		
Candy	8
Rabbit	1
Vanilla	1		

It is interesting to note that two of the chief offenders, wheat and milk, consistently measured up to the significance attributed to them by the skin tests. The same was true with pork. This is fortunate, since with wheat, milk and other foods eaten daily, the sensitization reaction furnishes a valuable aid toward their recognition.

The most frequent foods causing migraine, in order of importance (Columns 2 and 3), were found to be wheat, milk, peanut, chocolate, pork, pea, bean, onion, egg and banana, with a wide scattering of other foods. Sixty-two different foods were found definitely to cause headaches.

It is reasonable to anticipate that with the attacks reduced in frequency and with the patient on the alert he will himself discover additional foods causing his migraine, foods which had failed to react positively on testing. Column 3 lists these foods which were discovered by the patient, who had been advised to keep a food diary with this end in view. It is interesting to note that, with few exceptions, the foods in this particular list are such as are eaten only occasionally and could, therefore, be more readily discovered.

This is entirely analogous to the author's experience in a survey of 100 so-called nonallergic individuals, among whom were found 15 who had in the past suffered from headaches which they attributed definitely to certain foods. Here again the foods were such as are usually eaten infrequently and their recognition was thereby greatly facilitated. Had each been sensitive to several foods, or had they been so unfortunate as to become sensitive to foods eaten regularly, they too would have become chronic migraine cases. But, the cause having been recognized, they have practised avoidance, are symptom free and are considered nonallergic. Of the 15, 1 each was sensitive to peppers, cabbage, peanut, chocolate, cheese and egg; 2 each to cauliflower, onion and candy and 3 to watermelon.

The question of idiosyncrasy to candy is of great interest. Brown⁹ has concluded that carbohydrate intolerance is a distinct factor in the causation of migraine. Many carbohydrate foods contain protein moieties to which one may be sensitive and which could explain apparent carbohydrate intolerance. But can we say the same of candy? Eight patients in the author's series found from experience that candy caused migraine. Could there be noncarbohydrate allergenic substances in their favorite candies? The author has no information as to the favorite candies, but it is of interest that of these 8 cases 2 were sensitive to chocolate, 1 to almond, 1 to cocoanut and 1 to peanut. The remaining 3 had not been found sensitive to any of the common ingredients of candies. This leaves the question in the air for the present, but strongly suggests that more thorough analysis might demonstrate that it is not the carbohydrate of the candy which is responsible for attacks.

Proposed Method of Study of Migraine Cases. In concluding, the author would like to present a program for the systematic analysis of a case of migraine from the point of view of allergy.

1. Have a very comprehensive discussion with the patient, covering the details of the symptomatology, and careful questioning regarding other allergic manifestations in himself and in his direct family inheritance. Where such other evidences of allergy are demonstrated, the case should be studied with special intensity from the allergic point of view. There should be a listing of the frequency with which different foods are eaten. Onion, cabbage and egg, for example, may be eaten only occasionally by one person

but may be practically staple foods for another. After foods have been listed as to frequency, as daily, weekly, monthly or occasionally, a comparison of the lists with the stated periodicity of the attacks may give suggestive information. Remember, however, in this connection that sensitization is usually multiple in the chronic allergic. The discussion with the patient should also cover non-allergic factors such as fatigue, worry, excitement, catamenia, eye strain, etc.

2. Make careful sensitization studies in accordance with the latest approved methods, paying considerable attention to the borderline and delayed reactions. Two years ago a patient who had given 25 borderline reactions, and no strongly positive ones, informed the author that every one of the borderline reactors caused trouble. The author immediately suspected that suggestion was playing a part, although, knowing the patient, it was found difficult to believe. In view of the foregoing analysis, there was little doubt that she was correct.

3. Have another discussion with the patient explaining the findings and their significance, outlining the program and insisting upon the absolute necessity of coöperation. The experience that male patients do better than females illustrates the value of coöperation. One must be very positive in the outlining of the program. Eight years ago the author examined an asthmatic lady and, finding her sensitive to milk, advised that she eliminate this from her diet. She was not seen again professionally. A few weeks ago she said that during the last year she had left milk completely out of her diet and that she was now well. She remarked that now you could not make her touch a glass of milk, while up to a year ago she was so fond of it that she regularly drank many glasses daily. "But," I said, "it was 8 years ago that I told you to avoid milk." To which she replied, "I didn't think you were really serious. If you had said *positively*, I should have done it then."

4. Instruct the patient in the keeping of a food diary, to discover other causative foods which failed to show up on testing.

5. Make every effort to control nonspecific complicating factors, especially emotional and fatigue factors.

6. This is most important: Insist upon the absolute necessity for periodic supervision, of diminishing frequency if the case is progressing satisfactorily, but with annual checkups over a period of years, in an effort to discover and remove new factors, both allergic and otherwise, as they arise.

It is not the intention to imply in this discussion that every case of migraine is exclusively allergic. Migraine in the last analysis is but a symptom. But the author is firmly convinced that allergy is at least one factor in the vast majority of cases, and that with improved methods the results from allergic therapy, which are now most promising, will undoubtedly be still further improved.

Summary. The late results of the treatment of migraine from the standpoint of allergy are presented, on the basis of 63 cases, together with an analysis of the clinical data and the factors which seem to have influenced these results. A proposed method for the routine study of migraine cases is outlined.

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**COMPARATIVE ACTIONS OF SYMPATHOMIMETIC COMPOUNDS:
THE CIRCULATORY AND LOCAL ACTIONS OF THE
OPTICAL ISOMERS OF META-SYNEPHRIN AND
POSSIBLE THERAPEUTIC APPLICATIONS.***

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IN a recent paper¹ we pointed out the high order of activity of racemic meta-synephrin (metahydroxyphenyl-1-methyl-amino-2-ethanol-1) as a pressor drug and its low relative toxicity, and suggested that it might have therapeutic value. Recently, we obtained the levo- and dextro-isomers of this compound and its ketone, through the coöperation of Frederick Stearns & Co. The circulatory actions of these isomers have now been studied with the aim of determining their pressor efficiencies and mechanisms and some other actions, and of comparing them with the racemic mixture, previously reported.¹ The opportunity has also been taken to investigate various actions of meta-synephrin in human subjects, and to indicate its possible field of therapeutic usefulness.

* Supported in part by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

The racemie and dextro-compounds and the ketone were used in the form of hydrochlorids, while the levo-isomer was used as the tartrate and hydrochlorid. In comparing the activity and dosage of the levo-compound with the others, a correction must therefore be made for the lower meta-synephrin content of the tartrate salt. The levo-meta-synephrin base was reported by the manufacturers to have an optical rotation of -55.33 degrees at 20° C., while the dextro-base had $+50.4$ degrees. The dextro-base was, therefore, not entirely free of the levo-form. The corrected melting points were as follows: Levo-tartrate, 168° C.; dextro-hydrochlorid, 141.8° C.; racemie hydrochlorid, 142.2° C., and ketone hydrochlorid, 224.6° C.

Circulatory Actions. Cats. The control blood pressure and the pulse rate changes were recorded by the usual methods in urethanized cats, atropin being previously injected to permit elicitation of full pressor responses. Levo-synephrin tartrate was injected intravenously in doses ranging from 0.025 to 0.075 mg. per kilo, with resulting blood pressure increases of from 27 to 82 per cent. In 9 cats, the ratio of pressor activity of this isomer to the activity of epinephrin was a median of 5.15, range from 2 to 10. When this is expressed in terms of the hydrochlorid salt the ratio becomes 4.3. The dextro-isomer was much less active, doses of 0.5 to 1.5 mg. per kilo intravenously giving blood pressure increases ranging between 21 and 72 per cent. The median ratio of activity to epinephrin of this compound was 184, with a range of from 50 to 400. From these two ratios the racemie meta-synephrin would be expected to have an activity of about 8.5. The ratio of activity to epinephrin of the racemie, which was 5.6¹ is greater than can be accounted for by an additive action of the two isomers. This might be interpreted as evidence of a sensitization occurring in the racemic mixture. However, this cannot be accepted unreservedly, since the sum of the average deviations of the individual ratios from the two means is about equal to the observed differences between the means. The differences found are therefore statistically unreliable. The ketone was rather weak and variable in producing rises of blood pressure. The ratios of activity to epinephrin ranged between 224 and 714, with a median of 433. This low activity was in keeping with that of the other ketones previously reported by one of us.^{2,3,4}

The duration of the pressor response to the two isomers was similar to that of the racemic form described previously,¹ that is, about 10 minutes. Constant responses were obtained to repeated injections if complete recovery of the blood pressure was allowed after each injection. The pulse rate was not altered by the levo-compound, but was increased an average of 10 per cent by the dextro-compound, and 14 per cent by the ketone. Since these cats were atropinized and had rapid pulse rates, the changes observed

do not necessarily indicate what the responses might be under other conditions.

In order to study the mechanism of the circulatory stimulation, the cats were cocainized by our usual technique.⁵ This procedure increased the average pressor responses to a given dose of epinephrin from 32 per cent (control) to 59 per cent, *i. e.*, almost doubled it. At the same time, the average control response to the dextro-isomer, or 34 per cent rise of blood pressure, was unaltered, and the average response to the ketone was practically unchanged (from 19 [control] to 17 per cent) by the cocainization. But with the levo-compound the effect was different; the average control rise was 47 per cent, before the cocain, and after cocain it was greatly increased, *i. e.*, to 78 per cent. That is, there was almost as much sensitization to this levo-isomer as there was to epinephrin itself. Such sensitization by cocain to a compound not containing the catechol nucleus is quite unique, since there is no other noncatechol compound known to us with similar reaction. It may be that the suggestion of a sensitized response of the racemic mixture, previously noted by us,¹ may have been a true effect partially masked by the presence of the dextro-isomer.

Ergotamin* was injected intravenously in an average dose of 0.7 mg. per kilo, which sufficed to paralyze the sympathetic vaso-constrictors; the average control, or 48 per cent, rise of blood pressure after epinephrin was reversed to a fall of 21 per cent. The average control rise of 55 per cent after levo-meta-synephrin was decreased to an average rise of 21 per cent, but was not reversed. Similarly, the average pressor response to the dextro-isomer fell from an initial increase of 42 per cent to an increase of 30 per cent, and to the ketone, from an initial increase of 21 per cent to an increase of 4 per cent. All the ketone responses were unusually variable, because of the low order of activity of this drug, and hence are not especially reliable.

From the results obtained it is seen that the pressor actions of these meta-synephrin compounds were affected by either cocain or by ergotamin; but none of the compounds was both sensitized by cocain and reversed by ergotamin, or was unaffected by both these alkaloids. Hence, these isomers did not act as pure sympathicotropic, or as musculotropic, stimulants,⁶ but rather were mixed in their actions, similarly to arterenol and some other compounds previously described.²

Patients. To determine the possible clinical usefulness of the pressor effects of racemic meta-synephrin, this compound was administered by various routes to patients, the changes in blood pressure, pulse rate and symptoms, if any, being observed until recovery to the normal condition occurred. In 7 patients intra-

* Ergotamin was used in the form of Gynergen-Sandoz, supplied by the manufacturer.

muscular injections of total doses of from 5 to 10 mg. caused prompt rises of systolic blood pressure, averaging 14 mm. for the 5-mg. dose and 36 mm. for the larger doses. The diastolic pressures were also increased, but to a lesser degree, average 23 mm. The pressor response began in 4 minutes, reached a maximum in 9 minutes, and required an average of over 45 minutes for return to the control level. Thus, there was a very persistent vasomotor stimulation. During the height of the rise of blood pressure, the pulse rate was slowed moderately, as would be expected from the action on the vagus.

The same dosages of meta-synephrin were injected subcutaneously in 14 patients. The average maximum systolic rise for the entire group was 30 mm., and the diastolic rise, 13 mm. The rises of blood pressure began in 8 minutes, reached the peak in 20 minutes, and returned to normal after 80 minutes. The vasomotor stimulation after subcutaneous injection was therefore not quite as prompt as after intramuscular injection, but was almost as great in degree and about twice as persistent. It is obvious, therefore, that this drug, in the doses injected, is capable of producing well marked and sustained rises of blood pressure. It might, therefore, be a desirable remedy in those conditions requiring circulatory stimulation, such as collapse, hemorrhage, accidents of anesthesia and spinal anesthesia, etc. There were no obvious deleterious effects from the doses employed, except possibly in 2 or 3 of the patients, who had especially marked circulatory responses, in whom there was precordial discomfort at the height of the blood pressure rises. Such discomfort is a common accompaniment of the pressor responses to epinephrin and ephedrin, and is not peculiar to meta-synephrin.

The responses to oral administration of the racemic compound were determined in 15 patients at bed rest, who received the required doses in capsules. The minimal effective dose was about 120 mg., or approximately 2 mg. per kilo. The maximum dose administered was 300 mg. or 4.1 mg. per kilo. Throughout this range of doses there was some variation in the degree of pressor responses in individual patients, as might be expected. However, the systolic pressure increased an average of 23 mm., for the entire group of patients, and the diastolic, 14 mm. Thus there was an increase in pulse pressure at the time of the maximum pressor response, but the pulse rate compensated for this increase by a slowing of 18 beats per minute (average). Calculation of the cardiac output by the formula of Liljestrand and Zander⁷ showed that there was an average maximum decrease of 21 per cent in cardiac output, due entirely to the greater degree of slowing. The highest rise of blood pressure observed was 89 mm., which occurred 2 hours after the administration. The onset of the pressor response was usually prompt, the peak occurring after about 30 minutes. At the end of

2 hours the blood pressure was still elevated 11 mm. (average), but some very persistent elevations lasting over 5 hours were obtained. Hence, the pressor response was of fairly long duration.

An especially noteworthy result was the absence of general symptoms during even the highest elevation of blood pressure. The most marked symptom observed was little more than an awareness of increased cardiac activity, so that, for all practical purposes, it can be said that this drug was free of the unpleasant side-actions characteristic of ephedrin.

Levo-meta-synephrin hydrochlorid was also tested by oral administration. The initial dose was half that of the racemic compound, but this dose was increased in successive groups of patients until a pressor response was obtained comparable to the average response of the group who received the racemic compound. It was found that 2 mg. of the levo-compound per kilo, or from 120 to 140 mg. total, gave the same average pressor curve as about 3.5 mg. of the racemic compound. That is, the racemic compound was somewhat more active than would be expected from its levo- content. The relative activity of these two isomers given orally in man therefore agrees with that observed after intravenous injections in cats, described above. The results with oral administration may be summed up by saying that from about 200 to 300 mg. of the racemic synephrin, or from about 120 to 140 mg. of the levo-synephrin, may be given by mouth with the expectation of producing a well marked rise of blood pressure which may persist for over 2 hours. This vasomotor stimulation is accompanied by either no symptoms at all, or much less disturbance than would be caused by an equipressor dose of either epinephrin or ephedrin. Meta-synephrin, therefore, has definite clinical pressor actions, which may be of therapeutic value when the drug is given orally, similar to, but more persistent than, when it is injected.

Antichemotic Effects in Rabbits. Epinephrin, tyramin, and some other compounds⁸ have the power partially or completely to prevent local inflammatory edemas. In the present study we determined the anti-edemic actions of meta-synephrin by observing its effects on the degree of swelling and the time of development of chemosis after the application of mustard oil to the conjunctiva in rabbits. Solutions of mustard oil, ranging in strength from 5 to 100 per cent, were made in olive oil. Each of 11 rabbits received 2 drops of a given concentration in one conjunctival sac and the progress of the responses was recorded until recovery set in. After an interval of several days each animal was given 2 subcutaneous injections, 2 hours apart, of 5 mg. per kilo of levo-meta-synephrin. With the first injection the same number of drops of the same solution of mustard oil as used for the control was dropped in the previously untreated eye. The responses were then compared with the control to determine whether the meta-synephrin modified the course of the reaction.

In the 6 rabbits that received concentrations of from 30 to 100 per cent mustard oil, there was only a slight inhibitory effect of the drug on the chemosis. In 4 of these rabbits the effect was indicated by a small, but definite, decrease in the degree of swelling, or a delay in the development of the maximum response. In the other 2 rabbits the conjunctival responses were about the same as in the controls. These concentrations of mustard oil were sufficiently strong to produce a severe degree of irritation, which would require a very powerful antagonist; but meta-synephrin was almost ineffective. In the 3 rabbits receiving the weaker concentrations of mustard oil, namely 5, 10 or 20 per cent, an antagonism was clearly demonstrable. Meta-synephrin delayed the development of chemosis from 1 hour (time for maximum effect in controls) to 3 hours, and decreased greatly the degree of swelling. With the 5 per cent concentration of mustard oil, the meta-synephrin completely prevented the chemosis. Therefore, meta-synephrin exerted a definitely antagonistic action on the milder degrees of chemosis.

Topical Applications in the Human Nose and Throat. Because of its power to constrict bloodvessels, a possible therapeutic field for usefulness of meta-synephrin would be for local application in the nose and throat to shrink congested mucosæ, relieve turgescence and facilitate drainage. Epinephrin and cocain have been established as useful agents for these purposes for many years. Epinephrin, however, is apt to cause an increase in swelling after the initial period of vasoconstriction, and the use of cocain has serious drawbacks, such as the possibility of addiction, and the unpleasant or dangerous systemic reactions which may follow its use. In the last few years ephedrin has sprung into prominence for these local uses. However, there are also several disadvantages in its local effects, such as the almost universal production of pain and irritation, with secondary swelling and engorgement, and the occasional unpleasant systemic reactions. Recently we suggested the use of *para*-synephrin locally in the nose and throat,⁹ as a result of studies in the Stanford Division of Oto-rhino-laryngology. This compound was as effective, in appropriate concentration, as previously used drugs, and was definitely less irritating than ephedrin. Since *meta*-synephrin has 21 times the pressor (vasoconstrictor) activity of the *para* compound,¹ it seemed desirable to test its local actions upon the nasal mucosæ.

Solutions of 0.5, 1 and 2 per cent were made in a physiologic saline solution containing 0.05 per cent chlorbutanol as a preservative. These solutions were instilled, sprayed or applied on a pack into one nasal cavity, while the other side was similarly treated with a 3 per cent solution of ephedrin as control. It was found that the 0.5 per cent concentration of meta-synephrin produced a good constriction in 2 minutes, indistinguishable from that of the 3 per cent ephedrin. This constriction lasted $2\frac{1}{2}$ hours, or $\frac{1}{2}$ hour longer than

the ephedrin. With the 1 per cent solution the constriction was maximal, occurred within 1 to 2 minutes, and persisted up to 4 hours, or about double the duration of ephedrin action. Use of the 0.5 and 1 per cent concentrations was accompanied by no detectable irritation or symptoms. A 2 per cent solution acted in $\frac{1}{2}$ minute, with a 4-hour duration, but with slight irritation.* These results indicate that the meta-synephrin, in 1 per cent strength, cause intranasal shrinkage as much as, or more than, a 3 per cent solution of ephedrin, and apparently without irritation. Thus far we have seen no deleterious effects from its use, and no reactions, either systemic or local, so that it would appear to have a definite advantage over ephedrin for topical applications. As compared with para-synephrin, the 1 per cent meta-synephrin gives a more complete shrinkage than the para-compound in stronger solutions, and would therefore be the drug of choice. Observations along these lines are being continued and will be reported elsewhere in due time.

Use in Infiltration Anesthesia. Another use for the vasoconstrictor action of meta-synephrin might be as an adjuvant to local anesthetics in infiltration anesthesia. An indication of the possible usefulness of the compound was obtained by testing the power of various strengths of meta-synephrin to prolong the effects of procain. For this purpose 1 per cent procain solutions were made up so as to contain levo-meta-synephrin in 6 different concentrations, ranging between 0.01 per cent and 0.2 per cent. Higher concentrations of meta-synephrin were not tried since even with 0.2 per cent a full systemic dose would be contained in only 5 cc. of the anesthetic mixture. As controls, 1 per cent procain alone, 1 per cent procain with 0.001 per cent or 0.002 per cent epinephrin, 0.002 per cent epinephrin alone, 0.2 per cent levo-meta-synephrin alone, and physiologic saline solution were used. Two-tenths of 1 cc. of each of the 12 solutions was injected with aseptic precautions into separate squares marked off on the skin of the forearm of a subject. The appearance of a wheal was considered as good evidence of a satisfactory injection. Each injected area was tested for anesthesia at brief intervals until sensation returned to normal. The subject on whom the observations were made, and who had, of course, to judge whether anesthesia was present or not, was kept in ignorance of the particular solution injected in each area. Several such experiments were carried out on 3 subjects; the accompanying table shows the average times of duration of anesthesia with each solution.

It may be seen from this tabulation that procain alone produced a local anesthesia lasting an average of 25 minutes, while the other control solutions gave more transient effects. With the procain-meta-synephrin mixtures, duration of anesthesia was about doubled.

* We are indebted to Drs. G. I. Roberts and F. W. Borden for making these observations.

There was, however, no increase in efficiency with the stronger solutions of the meta-synephrin, so that apparently even the weakest concentration tested produced the maximum effect obtainable from such a mixture. By contrast the weaker epinephrin-procain solution (0.001 per cent) gave a duration 3 times that of the procain alone, and the stronger epinephrin solution (0.002 per cent) gave a duration 5 times as great. It is, therefore, apparent that the synephrin has power to enhance procain anesthesia, but is weaker than epinephrin in this respect. The main advantage of the synephrin would appear to be that it is stable in solution and, hence, could be used in the ready-made anesthetic solutions, instead of requiring addition just before use, as is the case with epinephrin.

TABLE 1.—AVERAGE DURATION OF ANESTHESIA.

Solution used.	Duration in minutes.
Physiologic saline solution	8
l-m-synephrin, 0.2 per cent	11
Epinephrin, 0.002 per cent	20
Procain, 1 per cent	25
Procain, 1 per cent + l-m-synephrin, 0.01 per cent	50
Procain, 1 per cent + l-m-synephrin, 0.025 per cent	41
Procain, 1 per cent + l-m-synephrin, 0.05 per cent	42
Procain, 1 per cent + l-m-synephrin, 0.075 per cent	49
Procain, 1 per cent + l-m-synephrin, 0.1 per cent	52
Procain, 1 per cent + l-m-synephrin, 0.2 per cent	44
Procain, 1 per cent + epinephrin, 0.001 per cent	72
Procain, 1 per cent + epinephrin, 0.002 per cent	133

Effect on Blood Sugar. One of the actions of epinephrin, or of ephedrin, is to raise blood sugar, which may be of value in combating hypoglycemic conditions. Tests were made to determine whether meta-synephrin shared this property. Three patients were injected with 7.5 mg. and 2 with 10 mg. of racemic meta-synephrin, subcutaneously, after a 12-hour starvation period. Blood samples were taken at $\frac{1}{2}$ -hour intervals for 3 hours. An average blood pressure rise of 30 mm. resulted from the injections and lasted an average of over 100 minutes. But in none of the patients was there the slightest rise of blood sugar during the 3-hour period of observation. Dr. Myron Heyn has informed us in a personal communication that 6 mg. of the drug per kilo subcutaneously will produce increases of blood sugar of about 40 mg. per cent in rabbits. Since the dosage of 0.15 mg. per kilo used in our patients approached the maximum desirable from the standpoint of the circulation, it is apparent that the dose required for hyperglycemia, as seen in the rabbit, would be too great for use clinically. Therefore, it may be concluded that, from the therapeutic standpoint, meta-synephrin cannot be of use for its effect on the level of blood sugar.

Influence on Allergic Reactions. Anaphylactic Shock.* In order to test the power of meta-synephrin to antagonize severe anaphyl-

* We are indebted to Drs. Samuel H. Hurwitz and A. L. Wessels of the Stanford Allergy Clinic for the observations described in this section.

active shock, experiments were made on sensitized guinea pigs. Eight guinea pigs were sensitized by injecting horse serum 3 weeks previously. On the day of the test, 3 animals were given 3 mg. per kilo, and 5, 14 mg. per kilo of racemic meta-synephrin, intramuscularly. From 15 to 30 minutes later, they were given an intravenous shocking-dose of the antigen. Of the 8 guinea pigs, 6 (75 per cent) died within 10 minutes after the injection of the antigen, the lungs at autopsy showing the typical distention of fatal anaphylactic shock. The 2 remaining animals showed severe symptoms, but recovered. In several control series of guinea pigs, treated in the same way except for the meta-synephrin, the percentage mortality ranged from 65 to 80 per cent. Therefore, meta-synephrin was not effective in diminishing the mortality, or the symptoms, of anaphylactic shock in guinea pigs.

Asthma and Urticaria. Further tests were made on allergic reactions in 5 patients. In 3 of these, spontaneous attacks of asthma of the typical allergic type were present, associated with a previously demonstrated specific sensitivity to certain antigens. The other 2 patients had the same type of sensitivity, but their asthmatic attacks and urticaria had been induced by the injection of specific antigens during the course of a desensitizing treatment. The dosage of racemic meta-synephrin used varied from 10 mg. as a single dose to 2 doses of 20 mg. each, all being given intramuscularly. In none of these cases was the bronchospasm or urticaria ameliorated to a perceptible degree by the meta-synephrin. However, epinephrin, injected subsequently, promptly terminated the attacks in the usual manner. Apparently, therefore, meta-synephrin lacks the power to antagonize the symptomatic manifestations of anaphylactic shock in patients. This might have been predicted from the results recently obtained by Dr. Martha James, in this laboratory (to be published later), namely, that meta-synephrin failed to relieve the bronchospasm induced in perfused guinea pig lungs by typical bronchoconstrictor drugs. Thus there is no satisfactory experimental basis for using meta-synephrin in allergic conditions, unless it might act as a circulatory stimulant in case of collapse.

Discussion. The results described have established a number of interesting facts. From a fundamental standpoint, one of the most intriguing of these is the demonstration of cocaine sensitization to the pressor action of levo-meta-synephrin, and a failure to do so to that of the dextro-isomer. Inasmuch as these differences are qualitative, and probably not merely quantitative, here is a situation where optical isomerism modifies the fundamental nature of a pressor response, and not just its degree of intensity. This is contrary to a common conception of the relation of chemical structure to the pharmacologic action of such compounds, namely, that the chemical radicals determine the mechanisms of their actions. It has been previously pointed out by one of us that tissues show pronounced

selectivity of response to optical isomers, in the group of sympathomimetic amines^{3,4} and in the cocain¹⁰ group as well. The demand of the tissues that levo-isomerism be present, if maximum pharmacologic activity is to be obtained, stands as a challenge to the chemist to supply the chemical basis for such selectivity. Studies directed toward the solution of this problem would be of great importance for understanding of the cause and nature of direct tissue responses to drugs, and even of the indirect responses from stimulation of the nerves themselves.

Of interest from the therapeutic standpoint is the high order of circulatory stimulant (pressor) efficiency of meta-synephrin, whether the drug is given subcutaneously, intramuscularly or orally. At present there is no other available compound which, when injected in the small dose of 10 mg. or less, will produce clinically a sustained rise of blood pressure, such as was observed by us. Small doses of epinephrin will produce similar rises, but they are less sustained. We have previously shown¹ meta-synephrin to have a margin of safety 8 times that of epinephrin in equipressor doses, or 45 times the margin when figured from the absolute weight of the drugs. Ephedrin will produce a rise somewhat longer in duration, but requires at least 5 times the dose; it has deleterious side actions on the heart,¹¹ its administration cannot be repeated freely, and it is apt to cause unpleasant symptoms. None of these objections hold for the meta-synephrin. Postpituitary extract will produce a rise of blood pressure similar in height and duration to meta-synephrin, but pituitary induces a complicating coronary spasm¹² and cannot be used repeatedly. It would seem, therefore, that racemic or levo-meta-synephrin would be especially valuable in those conditions requiring maintenance of adequate levels of blood pressure, as in spinal anesthesia, operations, shock and collapse with circulatory failure.

The other valuable clinical application of the drug should be as a topical agent in the treatment of congested or turgescient membranes in the nose and other suitable regions. The property of shrinking these membranes is not peculiar to meta-synephrin, but is shared by many compounds. However, this new drug seems to cause the shrinkage with a minimum or no side actions or symptoms. Therefore, in the opinion of our clinical colleagues, who have critically evaluated its merit by parallel controls, it would seem to be definitely superior to epinephrin and ephedrin.

Consideration should also be directed to the comparative merits of meta-synephrin and the para-isomer previously studied by us.^{4,9} The conclusions from those studies were that para-synephrin could increase blood pressure in patients when it was injected intramuscularly in doses of 200 mg. or more. Meta-synephrin, by comparison, produces equally high and more persistent rises with 10 mg. doses. Subcutaneous and oral administrations of para-synephrin were inef-

fective. With the meta compound, subcutaneous injection is almost as efficient as is the intramuscular, and oral administration produces excellent rises, which are lacking completely with the para-isomer. Both are superior drugs for local application in the nose, the meta-compound producing an equal degree of action, but in lower concentrations. It follows that meta-synephrin possesses all the desirable clinical actions of para-synephrin, and to a greater degree, together with certain advantages. Therefore, it may replace the para-compound completely as a therapeutic agent.

Conclusions. 1. The levo- and dextro-isomers of meta-synephrin (meta-hydroxyphenyl-1-methylamino-2-ethanol-1), the racemic mixture, and the ketone were studied as to their pharmacologic actions and possible therapeutic uses.

2. All these compounds raised the blood pressure when given intravenously to atropinized cats, the ratios of activity of the hydrochlorid salts to epinephrin hydrochlorid being: levo-isomeric 4.3, racemic 5.6, dextro-isomeric 18.4, and the ketone 433.

3. The pressor responses to levo-meta-synephrin were sensitized by cocain, whereas the responses to the other compounds were unaffected. Paralysis of the sympathetic vasoconstrictors by ergotamin, which resulted in reversal of epinephrin action, decreased but did not similarly reverse the pressor responses to the meta-synephrin compounds. The combined results in cocainized and ergotaminized animals showed that these meta-synephrin compounds did not exert pure sympathicotropic actions as does epinephrin.

4. In patients, doses of from 5 to 10 mg. of racemic meta-synephrin hydrochlorid, injected intramuscularly or subcutaneously, caused persistent rises of blood pressure, without serious or unpleasant side actions. Oral administration of the levo-compound or racemic mixture in total doses of from 120 to 140 and 200 to 300 mg., respectively, caused increases in blood pressure, which were well sustained for 2 or more hours.

5. Meta-synephrin has a slight antichemotie action when given subcutaneously in large doses to rabbits.

6. Applied locally in the nose and throat, meta-synephrin proved to be a valuable decongestive drug, since it promptly reduced swelling and edema without irritation or after effects.

7. When added to procain solutions in maximum concentrations, meta-synephrin doubled the duration of local anesthesia produced, whereas epinephrin trebled it.

8. Meta-synephrin had no demonstrable effects on the level of blood sugar, allergic reactions and bronchospasms in experimental animals or patients.

9. The main field for clinical usefulness of meta-synephrin would seem to be as a systemic circulatory (pressor) stimulant, and as a locally acting vasoconstrictor on mucous membranes, as in the nose. For these purposes the racemic and levo-meta-synephrins should be of practically equal value, if used in equivalent dosage.

10. Meta-synephrin has all the demonstrated therapeutic actions of para-synephrin and to a higher degree, with the added advantage of being effective orally; therefore, it should be able to replace the para-synephrin as a medicinal agent.

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BLOOD PRESSURE IN YUCATECANS.*

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BLOOD pressure levels have long been used as an index of health or disease. Certain levels have been evolved as standards for normal pressures, and readings above and below these levels are regarded as abnormal. Many things have been shown to influence blood pressure levels, but nearly always these factors have been within the individual himself, for example, the vascular and cardio-renal efficiency or the normal or abnormal functioning of the endocrine glands, and but very little account has been taken of the environmental factors. A study of the influence of environment might lead to a more thorough understanding of some of the underlying causes of abnormal blood pressures.

It has long been the general impression that in tropical environments the general level of blood pressure is lower than in temperate or cold regions. While on a medical expedition to Yucatan during the summer of 1931, the author had the opportunity of mak-

* The observations on which this paper is based were made during the summer of 1931 by the "Third Medical Expedition to Yucatan," which was organized by the Department of Tropical Medicine of Harvard University and which worked under the auspices of the Carnegie Institution of Washington. The data will be more fully presented in a volume entitled, "The Peninsula of Yucatan. Medical, Biological, Meteorological, and Sociological Studies," by George Cheever Shattuck, *et al.*, which is to be published by the Carnegie Institution of Washington. In the same volume will be presented other data on blood pressure gathered independently in Yucatan by Shattuck.

ing a large number of blood pressure readings on Yucatecans of all ages.

As used in the text, the name Maya refers to that tribe of Indians living in Yucatan; Mestizo to a male of mixed blood, usually Mayan and Spanish, and Mestiza to a female of the same racial mixture.

An enormous mass of material, statistics, tables and curves may be gathered from the literature on blood pressure readings, but it is very difficult to correlate the readings from different observers and to arrive at any definite standard for comparison. In fact, standards of normal seem to vary considerably in various parts of the world, dependent on certain environmental influences, and what would be a distinct hypotension in one locality would not be considered so in another.

Method of Collecting the Data. A Tyco's sphygmomanometer of the spring type was used with a standard 12-cm. wide arm band. This was checked against a mercury column before and after the data were secured and a small corrective figure added. Practically all the readings were taken by one observer, with the patient in each case seated in a chair with the arm about on a level with the heart. Some of the patients were perfectly healthy individuals, while most of them had a variety of complaints. They represent the sick as well as the healthy. The systolic reading was taken at the appearance of the first sound, and the diastolic at the change in tone.

Observations. Readings were reported on 1066 Mayas and Mestizos, aged 15 years and over. These figures are massed and grouped in Table 1. Table 2 gives the blood pressure distribution by pressures for both races and sexes.

TABLE 1.—AVERAGES OF SYSTOLIC, DIASTOLIC AND PULSE PRESSURES ON MAYAS AND MESTIZOS OF BOTH SEXES OVER 15 YEARS OF AGE.
BASED ON 1066 CASES.

Ages.	15 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80 to 89.
Average systolic	112.0	112.4	119.4	122.5	130.7	132.6	132.1	132.3
Average diastolic	70.2	71.7	75.6	75.0	75.3	73.3	70.0	78.4
Average pulse	41.8	40.7	43.8	47.5	55.4	59.3	61.3	53.9
Number of cases	122	292	257	184	123	61	24	3

Consolidated Averages for All Ages.

	Both sexes.	Males.	Females.
Systolic	119.9	115.7	123.3
Diastolic	73.5	71.5	74.8
Pulse	46.4	44.2	47.5

It will be seen that in the consolidated group 68.4 per cent of all readings fall between 100 and 130 mm. of mercury, and that in the same range there were 59.6 per cent of the male Mayas, 69.7 per cent of the female Mayas; 66.5 per cent of the Mestizos and 72 per cent of the Mestizas.

Regarding 150 mm. as the upper limit of normal systolic pres-

sure, it will be seen that there were 6 per cent above this limit in the entire group. Within this group were: Maya males, 3.5 per cent; Maya females, 8 per cent; Mestizos, 2.8 per cent; Mestizas, 7.3 per cent.

TABLE 2.—DISTRIBUTION OF SYSTOLIC BLOOD PRESSURES OF MAYAS AND MESTIZOS OF BOTH SEXES OF OVER 15 YEARS OF AGE. BASED ON 1066 CASES.

Pressures.	70 to 79.	80 to 89.	90 to 99.	100 to 109.	110 to 119.	120 to 129.	130 to 139.	140 to 149.	150 to 159.	Over 160.
Number of cases	6	22	72	212	279	237	106	68	32	32
Per cent of total	0.6	2.1	6.7	19.9	26.2	22.3	9.9	6.2	3.0	3.0

Distribution of Systolic Pressures for Maya Males: 143 Cases.

Number of cases	3	10	17	32	29	24	17	6	2	3
Per cent of group	2.1	7.0	11.8	22.5	20.4	16.7	11.8	4.2	1.4	2.1

Distribution of Systolic Pressures for Maya Females: 335 Cases.

Number of cases	0	1	19	71	95	67	28	27	17	10
Per cent of group	0	0.3	5.6	21.3	28.4	20.0	8.4	8.0	5.1	2.9

Distribution of Systolic Pressures for Mestizos (Males): 245 Cases.

Number of cases	3	10	23	53	55	55	26	13	1	6
Per cent of group	1.2	4.1	9.4	21.7	22.4	22.4	10.7	5.3	0.4	2.4

Distribution of Systolic Pressures for Mestizas (Females): 343 Cases.

Number of cases	0	1	13	56	100	91	35	22	12	13
Per cent of group	0	0.3	3.8	16.3	29.2	26.5	10.2	6.4	3.5	3.8

Thus, the female systolic pressures average several points higher than those for males. There are more females in the abnormally high pressure groups and more males having systolic pressure below 100 mm. In these low groups were 20 per cent of Maya males and only 5.9 per cent of Maya females; 14.7 per cent of Mestizos and only 4.1 per cent of Mestizas.

Comparison With Standards Elsewhere. Tables of blood pressure figures are of value only in comparison with blood pressure figures which may be considered as a standard. Certain observations may be quoted from North America to give a temperate zone standard, and others from various places to give a tropical zone and Oriental standard.

Woley has given the variation of systolic blood pressure in 1000 cases in the United States. His average for males was 127.5 mm. and for females 120 mm. His readings were taken by palpation which would make them 3 to 5 points lower than if taken by auscultation.

Norris quotes a table of blood pressure averages made by Dr. J. W. Fisher of the Northwestern Mutual Life Insurance Company, in which the averages are given for 64,574 presumably healthy adults. The systolic average was 123.2, diastolic 80 and pulse pressure 43.2.

Symonds gives the blood pressure findings in 150,419 males,

accepted life insurance risks and in 11,937 females, accepted life insurance risks. His average for males of all ages was 127.6 mm. systolic; 83.5 mm. diastolic and pulse 44.1 mm.

Alvarez gives the average figures for 14,934 men and women students of all ages, 16 to 40 years. The men average 128.9 mm. systolic and the women 117.3 mm. systolic. These represent a rather highly specialized social group and it is questionable whether the figures could be considered as standards for a population as a whole.

Barach and Marks give the blood pressure distribution figures in 742 adult males between 15 and 30 years of age. The table of figures follows later.

Donnison has given the blood pressure findings in 1000 East African natives. His table of figures will appear later.

Hudson and Young have shown the distribution of systolic blood pressures in 1056 Arabians.

Ashford and Dowling have analyzed the blood pressure findings in 250 patients in Puerto Rico, and determined the average systolic pressure for males as 114.3 mm. and for females 120.1 mm.

Torgerson has recorded the blood pressure findings in 100 consecutive hospital patients in Puerto Rico. The average systolic pressure was 120.2 mm., diastolic 73.8 mm. and pulse pressure 46.4 mm.

Chamberlain has presented the averages of blood pressures of American soldiers living in the Philippines as 115 mm. systolic for 18 to 30 years of age, and 118 mm. systolic for over 30 years of age.

Foster made a record of blood pressures of foreigners and Chinese in China. His figures will be given later.

An attempt will be made to correlate the observations of these various authors and to compare them with our observations made in Yucatan. The easiest way to do this will be to group the figures from various places in tabular form.

TABLE 3.—AVERAGE SYSTOLIC BLOOD PRESSURE ACCORDING TO VARIOUS AUTHORS.

Author.	Place.	Ages.	Sex.	Race.	No. of cases.	Systolic.	Diastolic.	Pulse.
Woley . .	U. S.	15-60	M F	Amer. "	1,000	127.5 120.0		
Norris . .	U. S.	15-60	Both	"	64,574	123.2	80.0	43.2
Symonds . .	U. S.	15-	M	"	150,419	127.6	83.5	44.1
Alvarez . .	U. S.	16-40	M F	" "	6,000 8,934	128.9 117.3		
Ashford . .	Puerto Rico	15-	M F	P. R. "	250	114.3 120.1		
Torgerson . .	" "	All	Both	"	100	120.2	73.8	46.4
Chamberlain .	Philippines	18-30 over 30	M M	Amer. "	1,000	115.0 118.0		
Saunders . .	Yucatan	15-	Both	Yucatecan	1,066	119.9	73.5	46.4

Table 3 groups some of the consolidated averages from various authors. It shows the average for the Yucatecans to be from 4 to 8 points lower than the averages from the United States. Table 4 compares averages by age groups. This table of figures indicates that in the lower age groups the average Yucatecan systolic pressures are appreciably lower than those given for the United States. In the age groups above 50 years, however, the Yucatecan pressures tend to equal the figures from one source.

TABLE 4.—AVERAGE SYSTOLIC BLOOD PRESSURES BY AGE GROUPS:
VARIOUS AUTHORS.

Age groups.	1.	2.	3.	4.	5.	6.	7.
15 to 19	123.5	117.1	123.1	107.0	...	112.0
20 to 24	122	124.2	120.5	122.8			
25 to 29	124.5	121.6	126.4	110.1	115.0	112.4
30 to 34	125.1	122.1	126.1			
35 to 39	127	125.3	122.8	125.5	114.5	118.0	119.4
40 to 44	126.4	124.1	118.3			
45 to 49	130	128.2	125.5	113.2	119.5	...	122.5
50 to 54	130.2	127.7	109.8			
55 to 59	132	133.5	130.3	106.6	124.8	...	130.7
60 to 64	138	135.2	132.5	105.8	121.4		
65 to 69	132.7
70 to 74							
75 to 79	132.1
80 to 84							
85 to 89	132.3

1. Wolcy's figures for 1000 Americans.

2. Symonds' figures for 150,000 American males (last figure for ages 60 and over).

3. Norris-Fisher's figures for 64,000 Americans (age groups 16 to 17, 18 to 22, 23 to 27, etc.).

4. Donnison's figures for 1000 East African natives (last figure for age 60 and over).

5. Ashford's figures for 250 Puerto Ricans (last figure for age 60 and over).

6. Chamberlain's figures for 1000 Americans in Philippines (ages 18 to 30 and over 30).

7. Saunders' figures for 1066 Yucatecans.

The high pressures in the upper age groups in Yucatan come chiefly from cases of hypertension among the females, as shown in the distributional Table 2. It is usually stated that blood pressures for females average considerably lower than for males. Alvarez shows that in his observations on college students the systolic pressures for women average considerably lower than for men. He says: "In young women there seems to be a high degree of correlation between the incidence of hypertension and the presence of various signs and symptoms of ovarian hypofunction." He ascribes hypertension not to infections or to strenuous life but to an inherited peculiarity, the appearance of which can be suppressed in women so long as the ovaries function well. Norris, in commenting on the sexual differences in blood pressure, noted that females average lower up to 40 years when the average systolic pressure for women is 1 or 2 mm. less than for men up to the age of 40 years, and that after 40 years the systolic pressures of women are quite equal to those of men and may be even higher.

The idea of ovarian hypofunction having a relationship to increased arterial pressure might have a bearing on the higher blood pressure of the Yucatecan women as compared with men. This difference was especially manifest after 40 years of age. Menstrual disorders, too, occurred among the Yucatecan women much more frequently than one would expect, and it may be that many of these disorders of menstruation were based on an underlying ovarian hypofunction.

Table 5 shows systolic blood pressure distributions from various sources. For Americans in the United States the greatest number of systolic pressures are found in the 120 to 129 mm. group and about 71 per cent are between 110 and 140 mm. My figures for Yucatecans show the largest number in the 110 to 119 mm. group, and about 68 per cent falling between 100 and 129 mm. This further substantiates the idea already brought out that the general average of systolic pressures is lower among the Mayas and Yucatecans generally than among North Americans. Hudson and Young's figures for Arabians show, however, the peak at the 100 to 109 mm. level with 68 per cent of the cases falling between 90 and 120 mm., or about 10 points lower than the Yucatecans. Foster's figures, too, show that for foreigners in China and Chinese in China the peak is at the 100 to 109 mm. level, with 72 per cent of the foreigners and 79 per cent of the Chinese falling between 90 and 120 mm. levels.

TABLE 5.—DISTRIBUTION PERCENTAGES OF SYSTOLIC BLOOD PRESSURES:
VARIOUS AUTHORS.

Systolic pressure.	1.	2.	3a.	3b.	4.
70 to 79	0.0	0.5	0.0	0.0	0.6
80 to 89	0.0	4.2	2.0	3.0	2.1
90 to 99	1.1	18.0	19.0	18.0	6.7
100 to 109	3.5	27.0	30.0	32.0	19.9
110 to 119	16.7	23.0	23.0	29.0	26.2
120 to 129	31.2	14.0	15.0	10.0	22.3
130 to 139	23.3	8.0	5.0	3.0	9.9
140 to 149	14.5	3.0	3.0	3.0	6.3
150 to 159	6.8	1.2	1.0	2.0	3.0
160 to 169	2.1	1.6	2.0	1.0	1.5
170 to 179	0.4	0.0	0.0	0.0	1.5

1. Marks, B. G.: Blood pressure in 656 adult male Americans.

2. Hudson and Young: Blood pressure in 1056 Arabians.

3a. Foster: Blood pressure in 120 foreigners in China.

3b. Foster: Blood pressure in 273 Chinese in China.

4. Saunders, G. M.: Blood pressure in 1066 Yucatecans.

It has been made clear that systolic blood pressure averages for Yucatecans range lower than systolic pressures in the United States, and slightly higher than in certain other places in the tropics or in China. It has been variously stated that in a tropical climate blood pressures range lower than in a temperate or cold climate, and practically all observations have tended to bear out the truth of this assertion. Ashford and Dowling's figures show a lower average for 250 Puerto Ricans. Torgerson's figures show a slightly lower average for 100 Puerto Ricans; Donnison's figures for African

natives show a lower average; Hudson and Young's figures for Arabians show a lower average, and Fleming states that the average systolic pressure of Americans living in the Philippines is 10 mm. less than the average of those in the temperate zone. Although he says "the blood pressures of Americans living in the Philippines differs little, if any, from the average at home." Chamberlain gives the figures for Americans in the Philippines as: systolic pressure average 115 mm. for 18 to 30 years of age, and 118 mm. for over 30 years of age. By referring to Table 3 these averages are seen to be distinctly lower than those of Woley, Norris, Symonds and Alvarez for Americans living at home. Roddis and Cooper studied the blood pressures of 173 American naval officers temporarily resident in the tropics, and stated that the systolic pressures averaged 11.5 points and the diastolic 11.2 points lower than the standard for the temperate zone, and that the average systolic pressure of 16 of those studied increased 9 points within a month after returning to the temperate zone.

It would appear, then, that in the tropics systolic pressures average lower than in temperate zones, though whether by virtue of climate or other environmental factors is not clear.

The observations from China showing low systolic pressure averages would tend to indicate that other than climatic influences are at work, for China is not a tropical country. Foster has stated that the blood pressure of a series of Occidentals living in China showed that the average for foreigners was about the same as that of the local Chinese, and that the blood pressures of the majority of the persons studied were lower in China than in America. Tung, in discussing the relative hypotension of foreigners in China, showed that 58 Americans, after residing 1 year in China, had a systolic pressure average of 9 points lower and a diastolic pressure average of 11 points lower than previously. He says that "the perpetual rush, tension and excitement that characterizes American life, and the comparatively slower and calmer life in Peking, although the work here may be no less strenuous, may be important factors in the causation of the relative hypotension."

Cadbury concluded from his studies that the blood pressures of Cantonese students from two of the southern provinces of China were lower than blood pressures of a corresponding group of Americans and Europeans of the same age, height and weight.

The reason for the lower systolic pressures among the Yucatecans is not clear. The warm climate probably plays an important part. Dally states that "in temperate climates a continued spell of warm weather frequently results in reducing the maximal pressure by 10 to 20 mm.; the contrary effect being produced by cold."

Fleming explains the lower systolic pressures of Americans in the Philippines as due to decreased peripheral resistance to circulation due to climatic factors. Roddis and Cooper ascribe these

lower systolic findings to climatic influences. The slower, more placid life in Yucatan is probably contributory. Foster, discussing lower pressures in China, feels that there may be a subconscient adjustment to the unhurried life of the East that lowers general tone. The life in Yucatan is certainly unhurried when compared with that in North America or Europe.

The height and weight of the Yucatecans may have some bearing on the lower blood pressures. Williams has shown that Yucatecans have lower height and weight standards than Americans and Europeans, and Synonds has demonstrated that blood pressures increase with height and weight. The women of Yucatan are generally more obese than the men and seem to have higher blood pressures.

The common occurrence of low grades of anemia among the Yucatecans probably does not influence the blood pressure. Norris states that "blood pressure bears no constant relation either to the percentage of hemoglobin or to the total number of corpuscles." Torgerson has shown that anemia does not appear to influence the blood pressure in Puerto Rico.

The occurrence of infections of various kinds may play some part in lowering the blood pressure of Yucatecans. Malaria cannot be a very important factor in Yucatan because its incidence there is low, but on the other hand the average systolic pressure in 28 persons whose blood showed plasmodia was only 104.6 mm., as compared with 119.9 mm. for the whole group of cases. Norris says that in chronic malaria hypotension is the rule.

Ascariasis is very common in Yucatan, probably 80 per cent of the population being infested. Dally states that "by reason of intestinal disturbances produced by these parasites (ascaris) the general health becomes impaired, and low arterial pressure often results."

But, whatever the other reasons may be, the slightly lower blood pressures prevailing among Yucatecans as compared with North Americans at home are probably due chiefly to two factors: the tropical climate and the unhurried life of the people.

The attention here has been devoted chiefly to systolic pressures. For the sake of brevity, the tables of diastolic and pulse pressures were not included here, but it may be stated that the diastolic pressures of Yucatecans is constantly lower than standards from North America, and that pulse pressures range about the same.

Summary. 1. Systolic blood pressures on Mayas and Mestizos seem to range 4 to 8 points below normal standards for blood pressures in the United States of America.

2. Female systolic pressures averaged higher than those of the males.

3. Diastolic pressures also ranged lower than in the United States of America.

4. Systolic blood pressures were grouped chiefly about the 110 to 119 mm. level among the Yucatecans, as against the 120 to 129 mm. level for pressure in the United States of America.

5. Some interesting differences for age groups were also indicated by the figures.

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DIAGNOSTIC IMPORTANCE OF BILIARY CRYSTALS.*

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THE presence of cholesterol crystals in the duodenal contents of a patient with cholecystitis was first noted by Einhorn.¹ Since then, various investigators²⁻¹¹ have reported the finding of cholesterol crystals or calcium bilirubinate pigment or both in preoperative specimens of bile, in cases of cholecystitis with and without stones. Nevertheless, bile microscopy has not been employed as frequently as it should be, especially in those patients with a history of gastric symptoms and in whom a diagnosis of gall bladder disease cannot be definitely established by the standard methods of examination.

It was thought of interest to study the diagnostic value of the microscopic examination of preoperative specimens of bile in a group of proved cases of calculous and non-calculous cholecystitis.

* Read before the Section of Medicine of the New York Academy of Medicine, November 15, 1932.

While in many of these patients the history pointed to gall bladder disease, in some the symptoms did not indicate gall bladder pathology. Included in this series were also cases in which bile microscopy was the only means by which a diagnosis of gall tract disease could be established. This study was made with the aid of photomicrographs of biliary crystals, taken before cholecystectomy, and compared with photomicrographs of crystals from postoperative specimens of bile and scrapings of stones removed from the gall bladder.

Cholesterol crystals and calcium bilirubinate pigment are the crystalline elements most commonly found in the bile preoperatively in cases of gall bladder disease. Other types of biliary crystals are encountered less frequently.

Typical cholesterol crystals are very characteristic and easily recognizable, although occasionally it may be necessary to differentiate them from amino-acid crystals.¹² Atypical cholesterol crystals have also been observed in the duodenal contents,⁷ although their diagnostic significance has never been emphasized. These crystals are colorless and assume various forms, some even having the window pane shape of typical cholesterol crystals, but without the characteristic broken corner. The chemical composition of atypical cholesterol crystals has not been fully established. This subject is still under investigation.

Calcium bilirubinate pigment, sometimes termed "calcium bilirubinate crystals," should be grouped into two classes: (1) The brick red or dark brown amorphous masses; (2) the light brown or amber colored granules. Hereafter, the former will be referred to as the amorphous type, and the latter as the granular type of calcium bilirubinate pigment.

Calcium carbonate crystals were also observed in the bile preoperatively in 2 of our cases of cholelithiasis. These crystals were colorless, oblong in shape and were soluble in hydrochloric acid. In 1 patient (Case 3) the crystals were found after operation in the scrapings of the whitish elevated areas, on the outer surface of a cholesterol and calcium bilirubinate gall stone. In the other patient the calcium carbonate crystals were observed postoperatively, in the "white bile" which was removed from the gall bladder.

The method of procedure employed in examining the bile of our patients was as follows: The duodenal tube was passed, preferably, in the evening. On the following morning the fasting specimen of bile and the specimens obtained after the instillation of 2 ounces of a 25 per cent solution of magnesium sulphate, or 5 per cent solution of peptone, were collected and examined. Biliary crystals were usually present in the grayish, dark brown or brick red flakes found in the bile. It was not necessary to centrifuge the specimens of bile in order to obtain the crystals. No special significance was attached to the A, B, and C fractions of the bile, since biliary

crystals were found as frequently in the fasting specimen of duodenal contents as in the specimens obtained after the instillation of magnesium sulphate or peptone. Furthermore, crystalline elements were seen, preoperatively, in specimens of bile, even when "B" bile was not obtained, although the cystic duct was patent.

The blood cholesterol (Bernhard-Drekter method¹³) and the icterus index (Maue-Bernhard method¹⁴) were determined in all patients.

Sixty-nine of the patients in whom biliary crystals were found in preoperative specimens of bile came to operation. In 63 cases (91.3 per cent) cholelithiasis (including patients with choledocholithiasis) or cholecystitis without stones was found. The types of crystals and pigment which were present in the bile preoperatively in these 63 patients were similar to the crystalline elements observed in the scrapings of the calculi or the bile removed from the gall bladder, at the time of operation. In the remaining 6 patients (8.7 per cent of the series) no stones were found at operation, nor did the gall bladder appear macroscopically diseased.

The 69 patients operated upon were grouped as follows:

1. Forty-seven patients in whom the history was typical of gall bladder disease.

2. Twenty-two patients in whom the history of gastric symptoms did not point to gall bladder disease.

GROUP I. Specimens of bile, which were obtained before operation from the 47 cases in this group, revealed the following (Table 1): Numerous cholesterol crystals with little or no calcium bilirubinate pigment were found in 9 patients (19.1 per cent); a large amount of calcium bilirubinate pigment with few or no cholesterol crystals was present in 8 patients (17 per cent); numerous cholesterol crystals and an abundance of calcium bilirubinate pigment were found, in the same bile, in the remaining 30 patients (63.9 per cent). In 2 of these patients calcium carbonate crystals were also found. Cholecystography (oral method), as can be seen from Table 2, showed roentgenographic evidence of calculi or pathologic gall bladder in 39 (82.9 per cent) of the 47 patients in Group I. Normal cholecystograms were seen in the remaining 8 patients (17.1 per cent). At operation, cholelithiasis was found in 39 patients (83 per cent); cholecystitis without stones in 5 patients (10.7 per cent), and in 3 patients (6.3 per cent) no calculi were found, nor did the gall bladder appear grossly diseased.

GROUP II. Sixteen of 22 patients of this group complained of various gastric symptoms, with little or no abdominal pain. Preoperative specimens of bile in these 16 cases revealed cholesterol crystals, with little or no calcium bilirubinate pigment, in 4 patients (25 per cent); a large amount of calcium bilirubinate pigment, with few or no cholesterol crystals, in 4 patients (25 per cent); and numerous cholesterol crystals and an abundance of calcium bilirubinate pigment, in the same bile, in the other 8 patients (50 per cent).

amount of pigment observed in the bile. A few scattered crystals or a small amount of calcium bilirubinate pigment, occurring separately or together, has not much diagnostic significance. But numerous cholesterol crystals and a large amount of calcium bilirubinate pigment, separately or collectively, in the bile preoperatively does indicate in most patients a calculous or non-calculous cholecystitis. The proper interpretation of bile microscopy may be the only means of definitely establishing the diagnosis of gall tract disease. This has been illustrated in some of the case reports.

Although bile microscopy was of invaluable aid in our gall bladder cases, it was not always possible, by crystal morphology, to differentiate between calculous and non-calculous cholecystitis (Table 3). Of the 14 patients in whom cholesterol crystals with little or no calcium bilirubinate pigment were found in preoperative specimens of bile, cholelithiasis was present in 9 patients (64.3 per cent), cholecystitis without stones in 3 patients (21.4 per cent), and in 2 patients (14.3 per cent) no calculi or macroscopic evidence of cholecystitis were found. Of the 15 patients in whom calcium bilirubinate pigment crystals with little or no cholesterol crystals were seen in the bile before operation, cholelithiasis was found in 7 patients (46.7 per cent), non-calculous cholecystitis in 5 patients (33.3 per cent), and in 3 patients (20 per cent) no stones nor gross evidence of cholecystitis was found. Of the 40 patients in whom numerous cholesterol crystals and a large amount of calcium bilirubinate pigment were observed in the same bile preoperatively, cholelithiasis was present in 35 patients (87.5 per cent), cholecystitis without stones in 4 patients (10 per cent), and in 1 patient (2.5 per cent) no calculi nor macroscopic evidence of cholecystitis was found. In 2 of the patients with cholelithiasis calcium carbonate crystals were also present.

TABLE 3.—COMPARISON OF THE CRYSTAL MORPHOLOGY WITH THE OPERATIVE FINDINGS.

Cases.	Per cent.	Crystalline elements in preoperative specimens of bile.	Operative findings.
14	20.3	Numerous cholesterol with little or no calcium bilirubinate pigment	Cholelithiasis, 9 patients (64.3%) Cholecystitis without stones, 3 patients (21.4%) No calculi or macroscopic evidence of cholecystitis, 2 patients (14.3%)
15	21.8	Large amount of calcium bilirubinate pigment with few or no cholesterol crystals	Cholelithiasis, 7 patients (46.7%) Cholecystitis without stones, 5 patients (33.3%) No calculi or macroscopic evidence of cholecystitis, 3 patients (20%)
40	57.9	Numerous cholesterol crystals and large amount of calcium bilirubinate pigment together	*Cholelithiasis, 35 patients (87.5%) Cholecystitis without stones, 4 patients (10%) No calculi or macroscopic evidence of cholecystitis, 1 patient (2.5%)

* In 2 of these patients calcium carbonate crystals were also present in preoperative specimens of bile.



FIG. 1.—Patient S. A. Typical cholesterol crystals (preoperative specimen of bile).

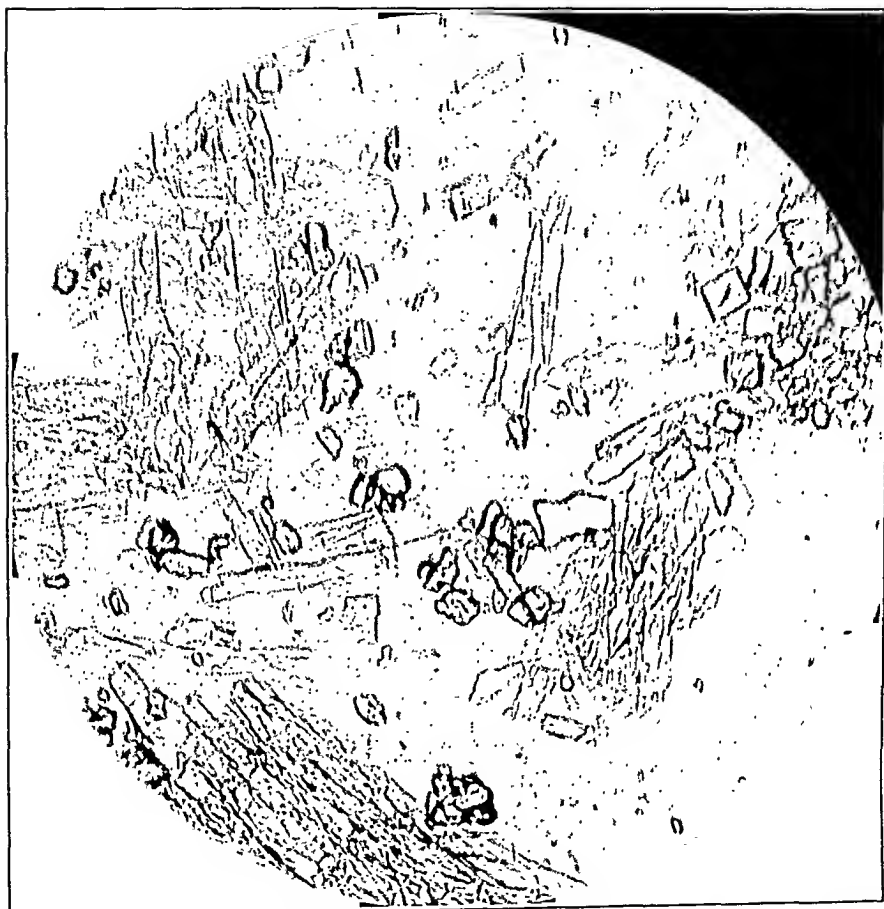


FIG. 2.—Patient S. A. Atypical cholesterol crystals (preoperative specimen of bile).

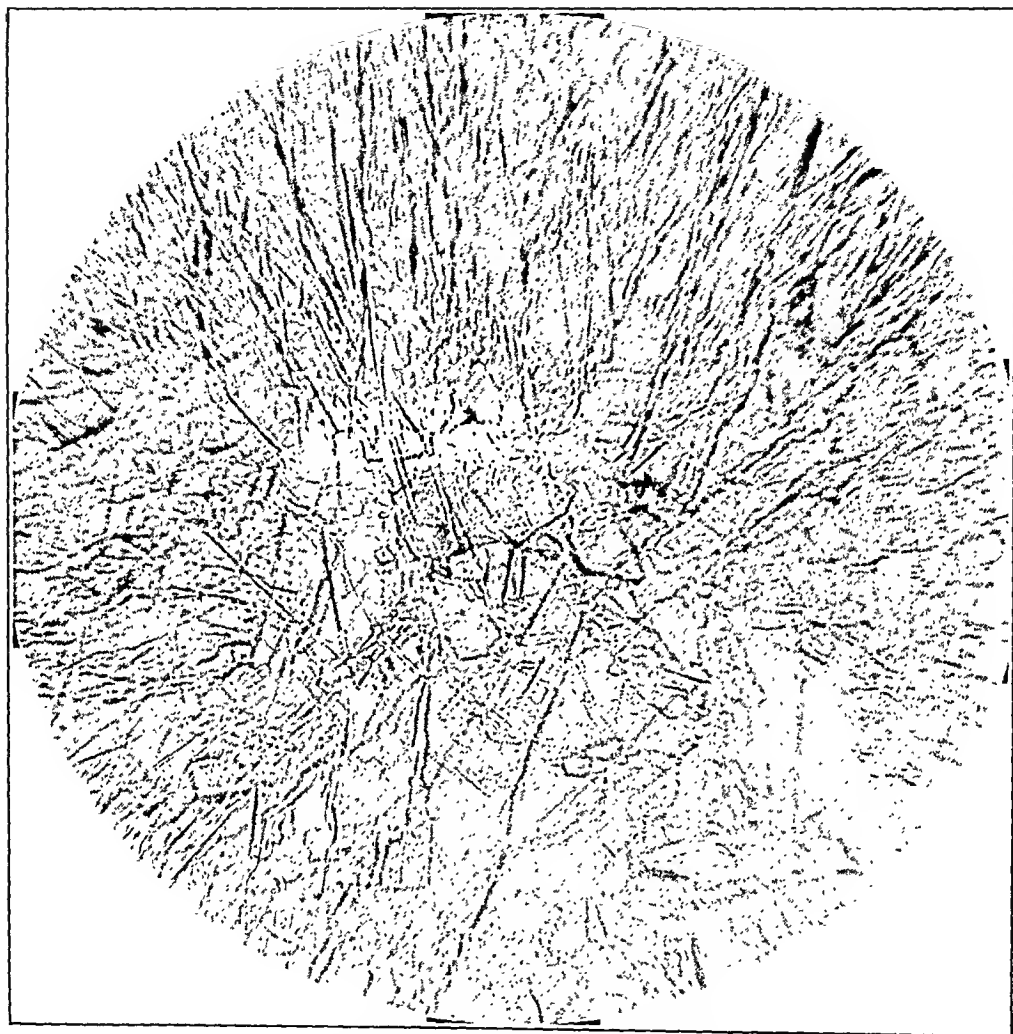


FIG. 3.—Patient S. A. Typical and atypical cholesterol crystals (scrapings of stone removed from gall bladder).

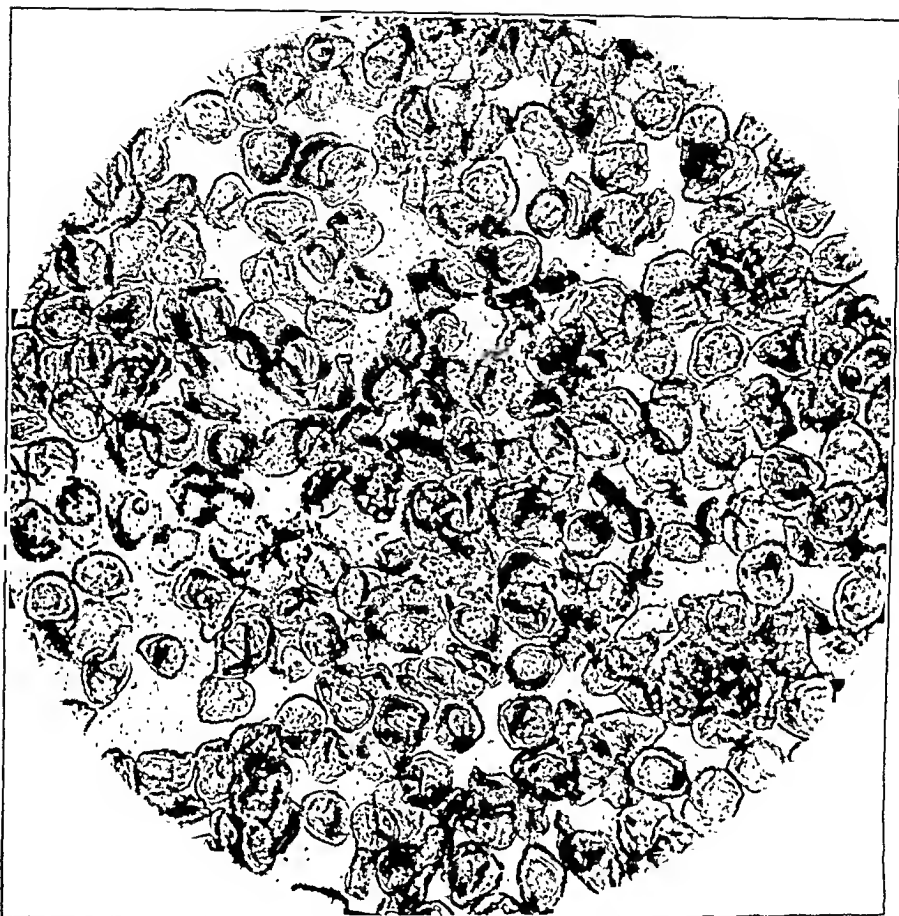


FIG. 4.—Patient Mrs. R. B. Calcium bilirubinate pigment—granular type (preoperative specimen of bile).

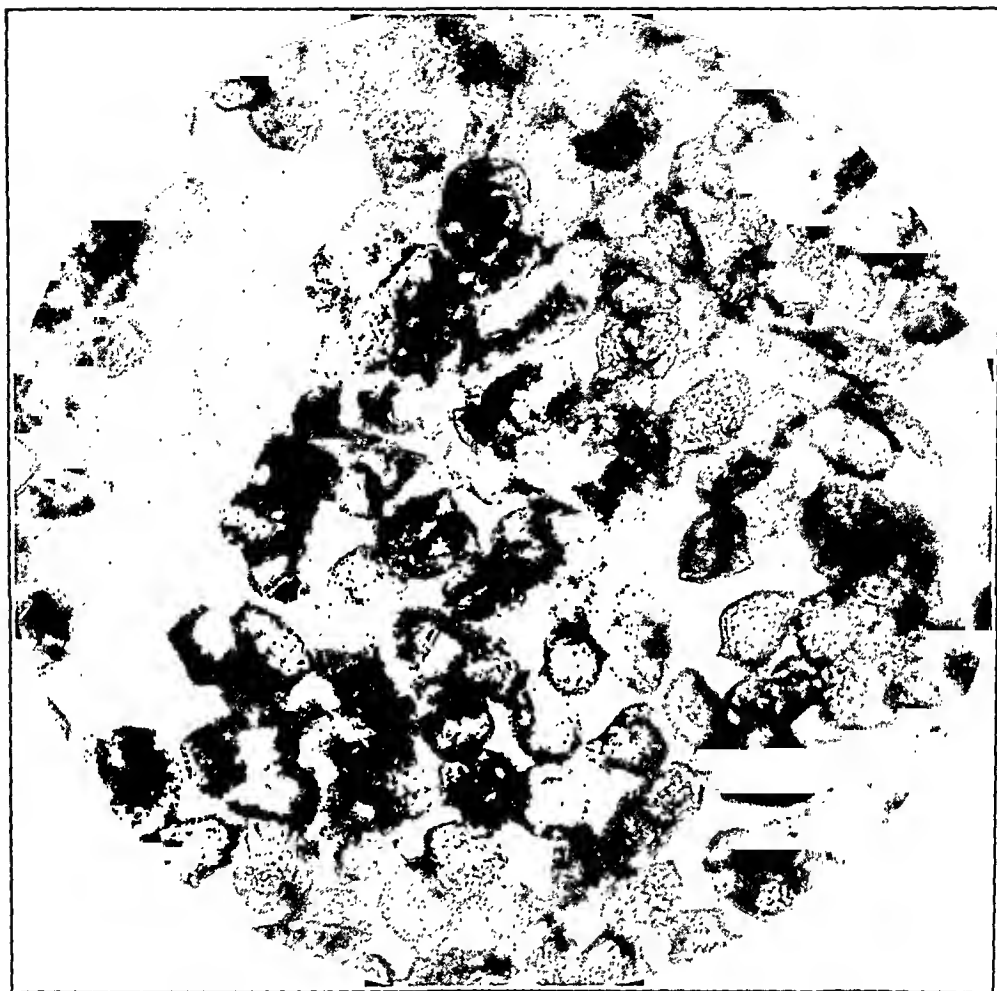


FIG. 5.—Patient Mrs. R. B. Calcium bilirubinate pigment—granular type (scrapings of stone from gall bladder).

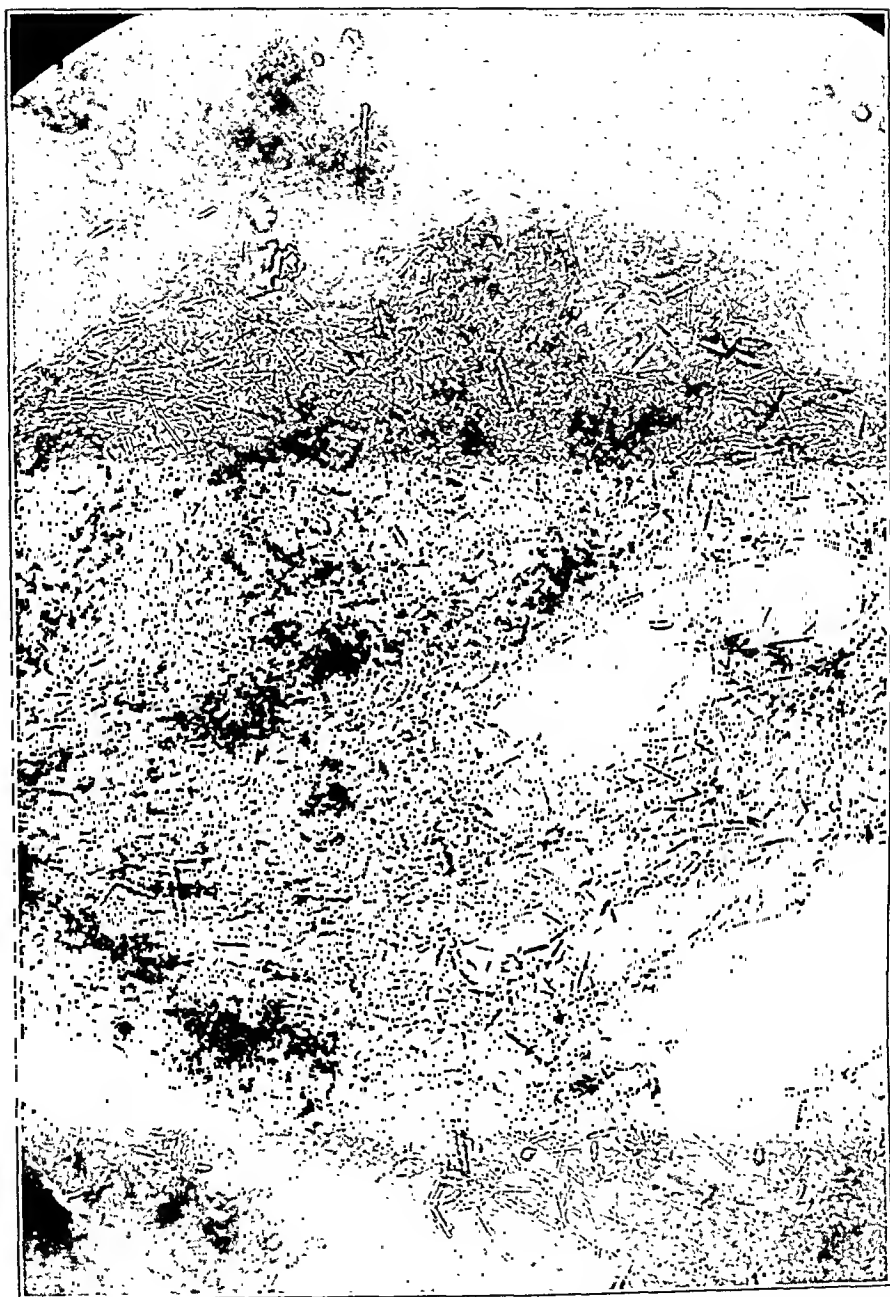


FIG. 6.—Patient B. G. Calcium carbonate crystals (scrapings from whitish elevated area of gall stone).

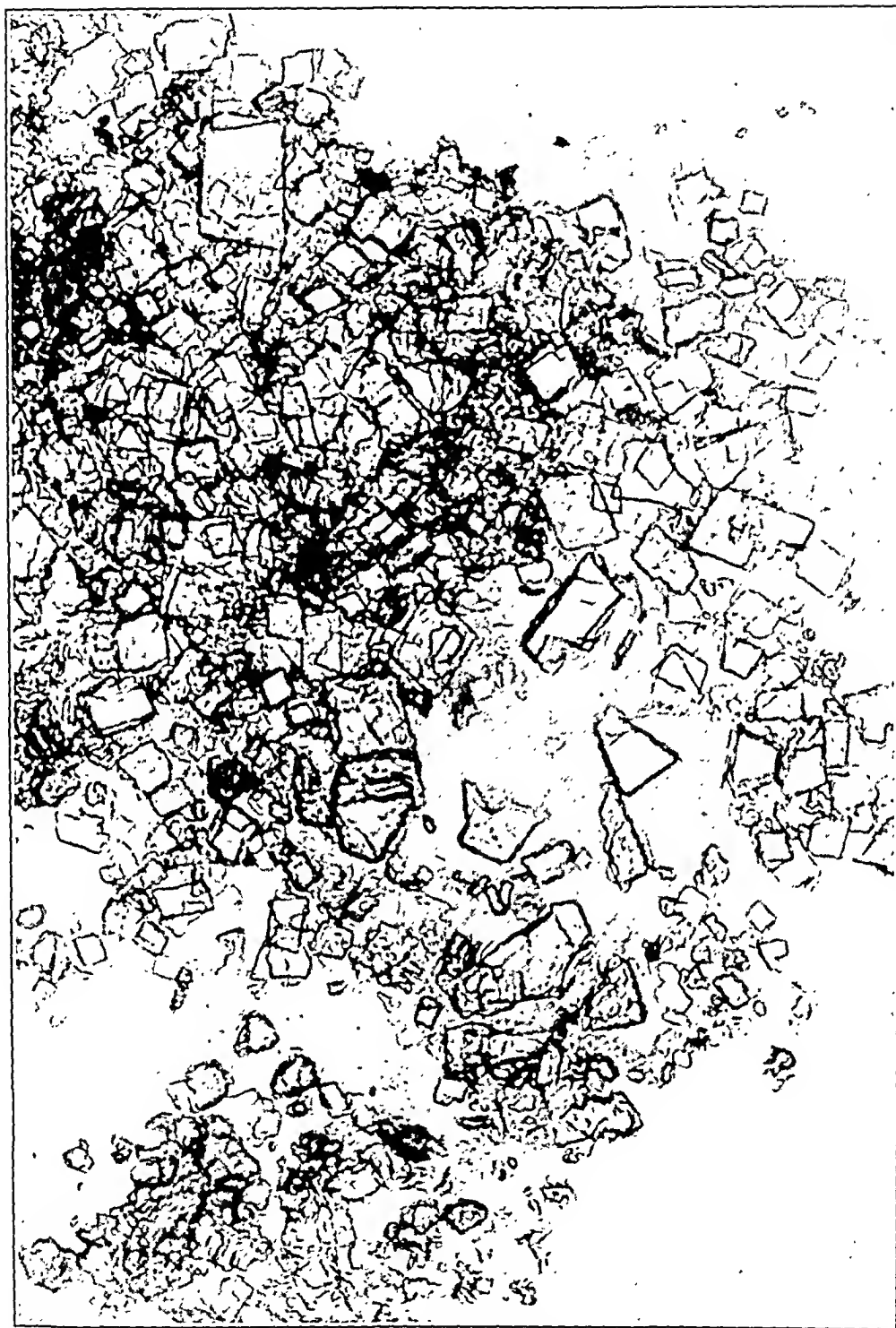


FIG. 7.—Patient N. S. Typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (preoperative specimen of bile).



FIG. S.—Patient N. S. Typical cholesterol crystals and amorphous calcium bilirubinate pigment (bile removed from gall bladder).

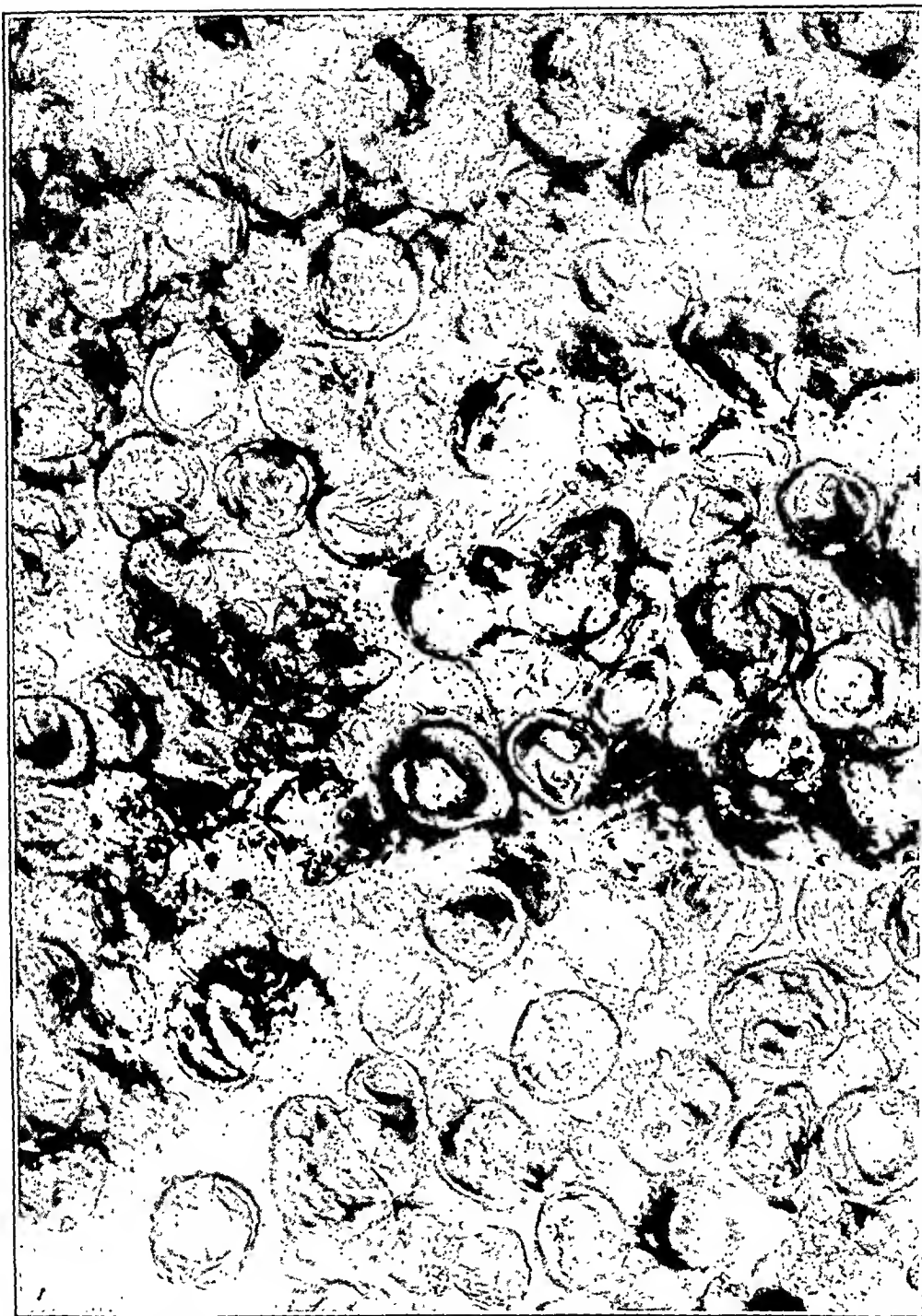


FIG. 9.—Patient Mrs. M. D. Calcium bilirubinate pigment—granular and amorphous types with the former predominating (preoperative specimen of bile).



FIG. 10.—Patient Mrs. M. D. Calcium bilirubinate pigment—amorphous and granular types (bile removed from gall bladder).

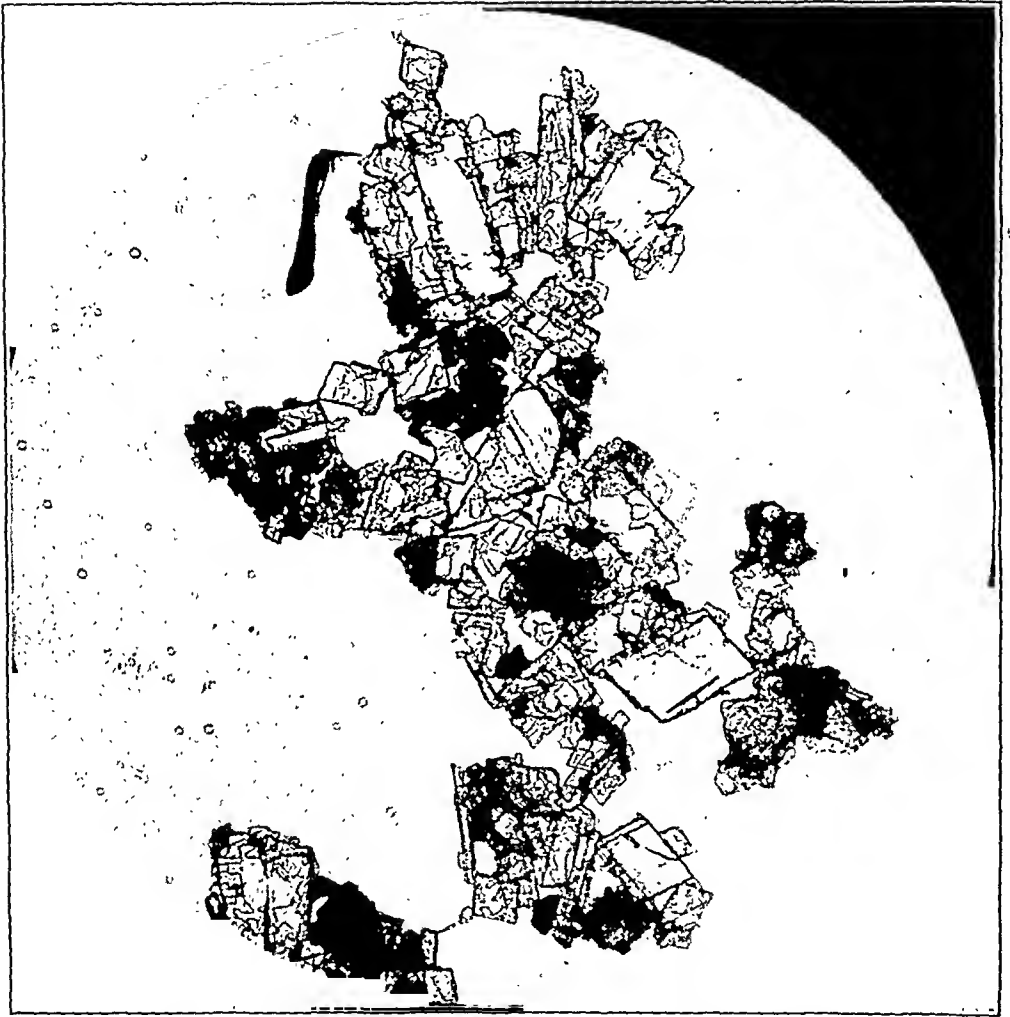


FIG. 11.—Patient P. D. Typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (preoperative specimen of bile).



The microscopic examination of the bile in our cases proved to be of more diagnostic value than cholecystography (oral method). As can be seen from Table 2, of the 69 patients who were observed there were 63 cases (91.3 per cent) of calculous and non-calculous cholecystitis which were detected by means of bile microscopy, whereas only 56 of these cases (81.2 per cent) were revealed by the cholecystograms. Similar findings were reported by Bockus¹¹ and his co-workers in their series of gall stone cases.

To summarize, it should be borne in mind that gall bladder disease is at times very difficult to diagnose. This is especially so in patients with a misleading history or negative roentgenographic findings, or both. Therefore, in an attempt definitely to eliminate calculous or non-calculous cholecystitis in doubtful cases, the patients should be given the diagnostic benefit of bile microscopy.

CASE 1.—Where the history, cholecystography and bile microscopy were in agreement.

S. A., male, aged 37 years, gave a history of attacks of biliary colic on and off for 3 years. Physical examination revealed an enlarged gall bladder. The icterus index was 7.2 and the blood cholesterol was 179 mg. per 100 cc. of serum. In the bile, numerous typical and atypical cholesterol crystals were seen (Figs. 1 and 2). Cholecystography revealed many non-calcified cholesterol calculi in the gall bladder. The patient was operated upon and numerous cholesterol stones were found. Upon examining the scrapings of the biliary calculi, typical and atypical cholesterol crystals were observed (Fig. 3).

CASE 2.—Where the history and bile microscopy were in agreement but the roentgenographic examination was negative.

Mrs. R. B., aged 33 years, gave a typical gall bladder history of 18 months' duration. Cholecystography revealed a normal functioning gall bladder. The icterus index was 6.5 and the blood cholesterol was 169 mg. per 100 cc. of serum. A microscopic examination of the bile showed many typical and atypical cholesterol crystals and calcium bilirubinate pigment—amorphous type (Fig. 4). The patient was operated upon and 12 small stones were found in the gall bladder and one in the common duct. When scrapings of the calculi were examined, they revealed similar crystalline elements as were seen in a preoperative specimen of bile (Fig. 5).

CASE 3.—Illustrates the calcium carbonate type of crystal.

Mrs. B. G., aged 65 years, complained of periodic attacks of pain in the right upper quadrant for 6 years. The bile showed many calcium carbonate crystals in addition to typical cholesterol crystals and calcium bilirubinate pigment. The Graham test revealed 3 calculi in the gall bladder. This finding was corroborated at the operation. The icterus index was 7 and the blood cholesterol was 287 mg. per 100 cc. of serum. Upon examining one of the stones, whitish elevated areas were seen on the outer surface. On rubbing one of these areas on a slide, calcium carbonate crystals (Fig. 6) were seen similar to those observed in the preoperative specimen of bile. The inner surface of the stone was composed of cholesterol crystals and calcium bilirubinate pigment.

CASE 4.—Illustrates a case in which bile microscopy was the only method of examination whereby the diagnosis was made.

Mr. N. S., aged 45 years, gave a history of periodic attacks of temperature and exhaustion about once every 6 months. He never had any abdominal pain, but complained of nausea and distention after eating. He rarely vomited. A physical examination was negative. Repeated examinations of the gastric contents revealed a persistent achlorhydria. Roentgen ray of the kidney, teeth, gastro-intestinal tract and gall bladder were negative. The icterus index was 5.6 and the blood cholesterol was 321 mg. per 100 cc. of serum. Bile microscopy showed numerous typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (Fig. 7). An exploratory laparotomy was performed. Six small calculi were found in the gall bladder. The bile from the latter showed similar cholesterol crystals and amorphous pigment as were seen in the preoperative specimen of bile (Fig. 8).

CASE 5.—Illustrates the fact that the diagnosis was definitely made by bile microscopy.

Mrs. M. D., aged 37 years, gave a history of having had a burning sensation in the epigastrium, on and off for 3 years. She never experienced any pain. The burning sensation at times would come on 2 hours after meals, and at other times there was no relation to food. A gastro-intestinal series showed a marked pylorospasm, but no definite deformity. At the end of six hours about one-fourth of the barium meal was still in the stomach. Gastric analysis showed free hydrochloric acid of 90; total acidity of 120; blood, positive. Cholecystography did not reveal any definite pathology. The icterus index was 4 and the blood cholesterol was 229 mg. per 100 cc. of serum. The patient had been treated unsuccessfully by various "ulcer cures" and, finally, an examination of the bile was made. It showed calcium bilirubinate pigment—granular and amorphous types (Fig. 9) and few typical cholesterol crystals. At operation no visible or palpable ulcer was found, but the duodenum was very much dilated. The liver was the seat of a marked fibrosis around the gall bladder bed. The gall bladder was very much thickened and adherent, but no stones were found. A cholecystectomy was performed. The bile from the gall bladder showed calcium bilirubinate pigment, granular and amorphous types (Fig. 10), and a few cholesterol crystals. The pathologic report of the gall bladder was "chronic catarrhal cholecystitis."

CASE 6.—Illustrates a case of a penetrating duodenal ulcer associated with calculous cholecystitis in which the gall bladder disease was definitely diagnosed by bile microscopy.

Mr. P. D., aged 34 years, gave a typical ulcer history, with pain 3 hours after meals and relieved by food. A gastro-intestinal series revealed roentgenographic evidence of a penetrating duodenal ulcer. Cholecystography showed a somewhat enlarged gall bladder which functioned very well. The icterus index was 6.2 and the blood cholesterol was 257 mg. per 100 cc. of serum. A preoperative specimen of bile, however, revealed many typical cholesterol crystals and calcium bilirubinate pigment in the same particle (Fig. 11). The patient did well for a time on medical treatment and then had a recurrence of his symptoms. This time the pain was more persistent and was not relieved by food. The patient subsequently came to operation. A duodenal ulcer and an enlarged gall bladder imbedded in a mass of adhesions were found. In the gall bladder there were 2 calculi, each about the size of a pea. A gastro-enterostomy and cholecystectomy

were performed. The scrapings of the stones and the bile from the gall bladder showed calcium bilirubinate pigment and cholesterol crystals as were seen in the preoperative specimen of bile.

Conclusions. 1. Various types of biliary crystals found in preoperative specimens of bile were compared with the crystalline elements found in the scrapings of calculi or bile removed from the gall bladder at the time of operation.

2. In 91.3 per cent of the cases the presence of these crystals in the bile, preoperatively, indicated calculous or non-calculous cholecystitis, irrespective of the history or radiographic findings.

3. Bile microscopy should be employed more frequently, especially in patients with a more or less persistent gastric history.

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REVIEWS.

ALCOHOL AND MAN. Edited by HAVEN EMERSON, M.D., De Lamar Institute of Public Health, Columbia University. Associate editors: HENRY A. CHRISTIAN, M.D., and REID HUNT, M.D., Harvard University; ARTHUR HUNTER, LL.D., F.A.S., New York Life Insurance Company; CHARLES C. LIEB, M.D., Columbia University; WALTER R. MILES, Ph.D., Yale University; ERNEST G. STILLMAN, M.D., Rockefeller Institute for Medical Research. Pp. 451; illustrated with tables. New York: The Macmillan Company, 1932. Price, \$3.50.

No substance that enters the human stomach has been more exhaustively studied or caused more acrimonious controversy than has alcohol. In the belief that "education in the basic facts about alcohol was essential to the best interests of modern man and his social organization, whether or not legislation was to be a permanent factor in determining the extent to which commerce in beverage alcohol was to be permitted," the authors have endeavored to "assemble and present for the use of the educated laity all the certain facts about alcohol in its biologic and human relationships which are well known and universally taught in the schools of medicine in this country today." They wisely have scrupulously avoided wet or dry advocacy or implications, being sanguine enough to believe that "all persons . . . will in rational periods of the fight pay attention to evidence." They are careful to add that none of the work has been supported in any way by wet or dry advocates. The effects of alcohol on man's conduct and mentality (chapters by Walter Miles, Adolph Meyer and Herman Adler) are treated in the greatest detail, but adequate consideration is also given to the physiologic and pharmacologic effects of alcohol, its effects on the cell and on heredity, on body resistance and longevity, its action as a poison and a medicine and the lesions that it produces. Making due allowance for individualities, one cannot but be impressed and aided by such authoritative statements as "On the brain alcohol in all doses is a depressant;" "most of the alcohol consumed is oxidized and supplies energy for the work of life;" "the habitual use of alcohol in moderate amounts . . . appears to be without any permanent organic effect deleterious in character;" "it is highly improbable that the quality of human stock has been at all injured or adversely modified by the long use of alcohol;" "the utilization of alcohol and alcoholic beverages . . . has decreased greatly and is continuing to decrease;" "total abstainers are . . . longer lived than non-abstainers; moderate users of alcohol : . . are probably as long lived as total abstainers."

E. K.

THE CHILD AND THE TUBERCULOSIS PROBLEM. By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., Professor of Preventive Medicine, University of Minnesota, Chief of the Medical Staff, Lymanhurst School for Tuberculous Children. With an Introduction by WILLIAM P. SHEPARD, M.D., F.A.P.H.A., Welfare Director, Western Division, Metropolitan Life Insurance Company. Pp. 230; 19 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.00.

This book will be of great value to physicians who have not had much experience in the field of childhood tuberculosis, to nurses, to all intelligent

public health officers, to social workers and particularly to school executives and other administrators who have to do with the health problems of childhood and youth. The author starts with the thesis that tuberculosis is a highly communicable disease to be controlled by the same methods as are effective in other contagious diseases, the first of which is prevention by stoppage at the source. He has departed from the old and still current view that tuberculosis in childhood, after recovery, immunizes sufficiently against further infection and is, therefore, to be looked upon as a protective mechanism inevitably attendant upon modern civilization. He cites many case records to prove his point, and clearly shows, out of the records of large experience in institutions with which he is connected, the manner in which childhood disease, so far from protecting against later tuberculous complications, actually prepares the way for the familiar adult disease. At the same time he points out the steadily lessening incidence of positive tuberculin reactions in children of many American communities, and urges the routine of frequent use of the tuberculin test in schools and in medical practice by family physicians as the most practical way to locate tuberculous infection early in its course when remedial measures can prevent it from passing into clinical disease. His argument on the small cost of early diagnosis as compared with the high cost of prolonged institutional treatment is thoroughly sound. The last chapter is a very able summary of the measures to be employed in an antituberculosis campaign of prevention. The book is of small but convenient size, excellently handled by the publisher.

E. L.

DISEASES OF THE SPINAL CORD. By WILLIAMS B. CADWALADER, M.D., Professor of Clinical Neurology, University of Pennsylvania Medical School, etc. Introduction by WILLIAM G. SPILLER, M.D., Professor of Neurology, University of Pennsylvania Medical School. Pp. 204; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$5.00.

THIS book is warmly commended by Professor Spiller, whose deep concern, in turn, is gratefully appreciated by the author. One would expect and finds much pathologic detail. At times it appears that the usefulness of the volume would be enhanced by more serious consideration of treatment. We are told: "The general practitioner will here find suggestions as to treatment," only to find it frequently discussed in a single sentence. A noteworthy exception is the treatment of acute anterior poliomyelitis.

Though highly scientific, the subject-matter is at all times concisely and lucidly presented and aptly illustrated throughout. There is an embodied wealth of opinion by others which is always carefully documented.

N. Y.

AN INTRODUCTION TO ZOÖLOGY. By ZENO PAYNE METCALF, D.Sc., Professor of Zoölogy, North Carolina State College. Pp. 425; 184 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.50.

THIS is a book of distinctive character, stressing function and using for detailed study as a type of the vertebrates, the rat. The author believed the use of a mammal preferable for students both as a better known type and as more significant for human biologic problems. The work is divided

into three parts, the first being introductory, the second dealing with the morphology and physiology of the rat and the third considering the philosophic implications of the facts disclosed. A constant effort is made to correlate structure and function. Each chapter is preceded by an analytical outline. The illustrations are numerous, of an excellent quality and mainly original. They are used to present structural details and to give an insight into general conditions difficult to describe briefly. There are a number of excellent and well-constructed diagrams of practical value, and a good index. Typographically the book is very pleasing. It should prove of great help to teachers who employ the author's method of presenting an introductory course in zoölogy.

C. McC.

DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID GLAND. By GEORGE CRILE and Associates. Pp. 508; 164 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.50.

THIS is not to be regarded as a formal treatise on the thyroid gland; "it is rather an account of the experience of the Staff of the Cleveland Clinic in the treatment of diseases of that organ."

The sections on iodine and the thyroid gland are exceedingly well written and covers a wealth of material in a relatively short space. In the chapter on The Role of the Thyroid Gland in the Energy System, the author postulates in a field which is as yet debatable. The chapter on Endemic Goiter is short but adequate. Carbohydrate metabolism in hyperthyroidism is well discussed by Dr. John. The sections on the clinical symptoms are written from a large clinical experience. While an entire chapter is devoted to the various blood pictures, hardly a page is given to basal metabolism. This is unfortunate.

The photographs and roentgenograms are excellent and better than some of the drawings illustrating operative procedures.

The book is valuable as giving the experiences of a large thyroid clinic. It could have been more carefully edited and would in numerous instances have been more convincing if certain material could have been presented as hypothetical rather than as experimental fact.

I. R.

MEDICINE AMONG THE AMERICAN INDIANS. Vol. VII of *Clio Medica*. By ERIC STONE, M.D. Pp. 139; 17 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.

ALTHOUGH they lived in a Stone Age culture, the American Indians in their medical practices were far in advance of the Stone Age, equaling, for example, the medical knowledge and practices of the Assyrians or the early Greeks. Moreover, their treatment of wounds, fractures and empyema was equal to or better than that of the white physicians of the 18th century, and in the management of retained placenta they anticipated Credé by a century. They added 59 drugs to our modern pharmacopoeia, including cascara and lobelia. Heretofore the material on the medical practices of the Indians has been hidden in short fragments under a mountain of other lore. In gathering this material for the first time under one cover—a task that has been very creditably carried out in this convenient pocket-sized volume—the author has performed a real service.

R. K.

MINOR SURGERY OF THE URINARY TRACT. By HERMON C. BUMPUS, JR., Ph.B., M.D., M.S., F.A.C.S., Associate Professor of Urology, The Mayo Foundation. With a chapter on Caruncles by JOHN L. CRENSHAW, M.D., Associate Professor of Urology, The Mayo Foundation, and a chapter on Postoperative Care by ANSON L. CLARK, M.E., M.D., Section on Urology, The Mayo Clinic. Pp. 124; 57 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$3.00.

THIS splendid little book details in great clearness the technical treatment of urologic conditions by instrumental methods. No attempts are made to outline symptoms or diagnostic steps; for it is intended for the guidance of one already proficient in these departments. The subjects covered are caruncle of the urethra, stricture of the urethra, hypertrophy of the prostate, carcinoma of the prostate, stone in the bladder, tumor of the bladder, bladder infection and ulcer, and stone in the ureter. One wonders, on the one hand, when such serious pathologic states are being treated, whether the term "minor surgery" is justified; while, on the other hand, it is a delightful commentary on the startling advances accomplished in this field in the last two decades through instrumental methods, for it is to this phase of therapy that this book is almost exclusively limited.

A. R.

LES RÉTICULOCYTES ET LES RÉTICULOCYTOSES. By DR. C.-M. LAUR, Préparateur Adjoint a la Faculté de Médecine de Paris. Preface by PROF. N. FIESSINGER. Pp. 160; 3 figures and 4 plates in colors. Paris: G. Doin & Cie, 1932. Price, 35 fr.

ALTHOUGH these immature erythrocytes have been recognized and studied in the circulation since the time of Ehrlich, it was not until the past decade that their great practical value in clinical medicine was realized in connection with Minot's work on the liver treatment of pernicious anemia. No extended systematic study, however, of their various manifestations and significance has been attempted until Fiessinger, the eminent French hematologist, stimulated the present work. This richly documented statement is divided into 6 chapters covering the history of the subject, technique, nature of reticulocytes and their behavior under normal and pathological condition. It should prove very useful to hematologists.

E. K.

THE COLON, RECTUM AND ANUS. By FRED W. RANKIN, B.A., M.A., M.D., F.A.C.S., Division of Surgery, The Mayo Clinic; Associate Professor of Surgery, The Mayo Foundation; J. ARNOLD BARGEN, B.S., M.D., M.S. in Medicine, F.A.C.P., Division of Medicine, The Mayo Clinic; Assistant Professor of Medicine, The Mayo Foundation; and LOUIS A. BUIE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic; Associate Professor of Proctology, The Mayo Foundation. Pp. 846; 435 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$9.50.

THIS monograph should take first rank in the literature on the lower bowel and anus. Extensive clinical and laboratory facilities have combined to give the authors an experience and grasp of the subject rarely equalled. The complete chapters on anatomy and physiology include a full discussion of the nerve supply of the bowel, a subject of increasing importance in these days of sympathetic nerve surgery. The various diseases of the colon, such as megacolon, volvulus, intussusception, diverticulitis, the

granulomata, etc., are treated in detail, while the chapter on chronic ulcerative colitis is largely a summary of Barger's extensive work in this disease. Because tumors of the large gut represent such a large portion of colon diseases their diagnosis and treatment have been fully discussed. Buie has added a well-written section on minor surgical diseases of the anus. A short, well-illustrated chapter by Lundy discusses anesthesia in operations on the large gut. In the final technical section are described and illustrated the various operative procedures which the authors use in the treatment of their cases.

The book should make a particular appeal to the general surgeon and to the gastro-enterologist, as the latest and most up-to-date work on its subject.

L. F.

SCIENTIFIC AND ESOTERIC STUDIES IN SEXUAL DEGENERATION IN MANKIND AND IN ANIMALS. By PROFESSOR CHARLES SAMSON FÉRÉ. Translated by ULRICH VAN DER HORST, Ph.D. Pp. 325. New York: The Falstaff Press, 1932. Price, \$6.00.

ACCOUNTS and discussions of sexual perversions are undoubtedly nasty reading for some people, and without emotional connotations for the objective scientist. But it must also be recognized that unfortunately they are pleasantly erotic for the pornographically minded. Their importance, however, in the pathologic physiology of sex cannot be overlooked on this account, and an ostrich policy toward the subject on the part of the medical profession will necessarily have the usual disastrous results. It seems obvious, then, that their distribution should be limited as far as possible to the appropriate scientific readers. This is apparently attempted for the present translation by restrictions placed on its sale, though it must be recognized that the type of its advertisement, cover and frontispiece, and the inclusion of "esoteric" in the sub-title do not tend to support this view. Except for this qualification, and perhaps a laxity of standard of observational control, we find no fault with the subject matter, though we may not agree with many of the opinions expressed. The number of observations on a great variety of animals are sufficiently correlated with human abnormalities of behavior to afford a valuable lateral attack on the evaluation of the latter. Just as comparative pathology is an important department in the study of somatic disease, so should proper investigations in comparative psychology lead to noteworthy advances in the field of psychiatry.

E. K.

CLASSIC DESCRIPTIONS OF DISEASE. By RALPH H. MAJOR, Professor of Medicine, University of Kansas School of Medicine. Pp. 630; 127 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.50.

THE potency of such works as this in enlivening acquaintance with the history of medicine has already been stressed in these columns in connection with Camac's Epochmaking Contributions, Long's Readings in Pathology and Fulton's Selected Readings. The more such anthologies are added to, if well selected and accurately edited, the more widely may knowledge of the master medical writings be spread among the medical profession and integrated, in the Oslerian manner, with the practical education of the medical student. Pursued through all the major branches of medicine, this method also will bring these gems to hundreds of centers that never could have attained possession of a like number of originals. The author is to be congratulated on the soundness of his selection, in fact the very

SURGERY

UNDER THE CHARGE OF

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Cholesterol and the Gall Bladder.—There has been a long controversy as to whether cholesterol is absorbed from, excreted into, or merely concentrated in the bile of the normal gall bladder. NAUNYN (*A Treatise on Cholelithiasis*, London, New Sydenham Society, 1896) supported the hypothesis that the gall bladder and extra-hepatic bile ducts secreted cholesterol into the bile. In this contention he was supported by his many students and associates. On the other hand, ASCHOFF (*Münch. med. Wchnschr.*, 1906, 53, 1847) and his school have maintained that cholesterol is absorbed from the bile through the gall bladder wall. Data on this controversial point are important because of the relationship which cholesterol bears to calculus formation.

Among those who have within recent years supported the Naunyn hypothesis are TORINOUMI (*Beitr. path. Anat. u. allg. Path.*, 1924, 72, 456), ILLINGWORTH (*Brit. J. Surg.*, 1929, 17, 203), BOYD (*Ibid.*, 1923, 10, 337) and ANDREWS, SCHOENHEIMER and HRDINA (*Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 945). Of the above papers Illingworth's conclusions were undoubtedly based upon insufficient data. Boyd did not actually measure the cholesterol content quantitatively and Andrews, Schoenheimer and Hrdina published no data for critical review. Torinomi, however, found that cholesterol was absorbed from the normal gall bladder but excreted into the infected viscus.

ELMAN and TAUSSIG (*Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 1006; *J. Exp. Med.*, 1931, 54, 775) and ELMAN and GRAHAM (*Arch. Surg.*, 1932, 24, 14) have reinvestigated this very important subject. These authors concluded that both the concentration and the total amount of cholesterol increased in the hepatic bile when it was subjected to the activity of the gall bladder. Their work is open to the criticism that in the dog their studies cannot be considered quantitative. However, their studies on the human are important in that in the presence of gall bladder disease they demonstrated that the gall bladder did secrete cholesterol.

RIEGEL, JOHNSTON and RAVDIN (*J. Exp. Med.*, 1932, 56, 1), after a study of the fate of cholesterol in hepatic bile when subjected to the activity of the normal gall bladder, concluded that cholesterol is not secreted into or absorbed from such a viscus. Their observations, which were made by a method which has been proven to be satisfactory for quantitative studies, led them to conclude "as did ROUS and McMASTER (*J. Exp. Med.*, 1921, 34, 47) with regard to bile pigment, that normally there is no absorption of cholesterol . . . save in the case of the infected gall bladder." In the infected gall bladder evidence was

obtained to support the observations of Elman and Graham. Since the papers of Elman and his associates and those of Riegel and her associates were published, two other papers have appeared which merit review. WILKIE and DOUBILLET (*Arch. Surg.*, 1933, 26, 110) propose an ingenious action of the gall bladder wall. If the bile cholesterol is high, absorption will occur from the bile to the blood; while if the blood cholesterol is high, the cholesterol will pass from the blood to the gall bladder bile. It should be pointed out that in quantitative experiments reported by Riegel, Johnston and Ravdin where the hepatic bile of the dog (with concentrations varying from 11 to 46 mg. per 100 cc. of bile) were subjected to the activity of the normal gall bladder, there was no evidence that such a mechanism existed and that when one considered the concentration of the hepatic bile after its entrance into the gall bladder no excess of cholesterol could be demonstrated even though it is well known that the blood cholesterol of the dog is high.

A more recent paper by ANDREWS, DOSTAL and HRDINA (*Arch. Surg.*, 1933, 26, 382) adds further evidence to the earlier observations of Riegel, Johnston and Ravdin as regards the normal gall bladder and to the evidence reported by Elman and Graham as regards the infected gall bladder.

THERAPEUTICS

UNDER THE CHARGE OF

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The Influence of Thyroxin on Avertin Narcosis.—It has been claimed that even relatively large doses of avertin fail to induce deep sleep in cases with hyperthyroidism. The intravenous administration of thyroxin as an antidote in severe avertin narcosis has also been suggested. The most reliable objective measure of the duration and depth of avertin narcosis is its concentration in the blood. NELL (*Klin. Wchnschr.*, 1932, 11, 367), therefore, undertook the measurement of the concentration of avertin in the blood and the duration of sleep in a group of control subjects, and in a second group which received 0.2 mg. of thyroxin $\frac{1}{2}$ hour or 1 hour after the administration of avertin. A third group of patients received the thyroxin 1 hour before the administration of avertin. In a fourth group thyroxin was administered in amounts that produced elevation of the basal metabolism alone, or in addition symptoms of thyrotoxicosis. From 0.1 to 0.125 gm. of avertin per kilogram of body weight was administered. On the basis of such a carefully controlled study the author claims that thyroxin in amounts described does not influence either the concentration of avertin in the blood or the duration of sleep. If thyroxin previous to

the time of anesthesia produces an elevation of the basal metabolism without symptoms, the duration of narcosis is shortened, not because of the increased rate of destruction of avertin in the body, but because of the low absolute concentration in the blood. Patients with symptoms of thyrotoxicosis, on the other hand, showed a deep and prolonged sleep with a corresponding high avertin concentration in the blood.

PEDIATRICS

UNDER THE CHARGE OF
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Diphtheria Control in Chicago.—BUNDESEN, FISHBEIN and NIBLACK (*J. Am. Med. Assn.*, 1933, 100, 1093) state that the diphtheria mortality in Chicago has been reduced by having nurses call on the parents of every child up to 8 years of age, urging that the child be taken to the family physician for diphtheria immunization and obtaining signed cards asking that the children be immunized. The maintenance of an active list of all the younger children in a community is most important in carrying out this as well as many other health programs. The authors have found it of extreme value in their diphtheria-prevention campaign. As soon as the child reaches the age of 6 months, a personal call is made on the mother. Continuing this routine it is likely that the diphtheria immunization will be brought to an even higher level and that the mortality and the morbidity rates be reduced to lower levels than have already been attained. It was found that with the alum toxoid a far lesser number of reactions occurred in the children; that there was a more rapid production of the immunity, and a greater percentage of the children became immune with two inoculations. In the light of present knowledge this seems to be the most efficient immunizing agent against diphtheria. In all communities in which there are a large number of foreign-born individuals the coöperation of the church influence proves invaluable in promoting all forms of public health work. Some of the individuals of these races, many of whom have suffered persecution of various types in the countries of their origin, show a tendency to resent what they consider interference with their personal liberty. This can be overcome by the influence of secular advice and it was found to be the greatest single factor producing the success of the reported campaign. The distribution of literature urging diphtheria immunization alone cannot be successful in stimulating the protection of a large proportion of the child population. Such literature has its greatest value in paving the way for the visits of the nurses, whose function should be that of salesmen selling diphtheria immunization. Needless to say the coöperation of the medical societies as well as of the individual physicians is necessary for the successful public health campaign.

An Unusual Encephalopathy Probably Infectious in Origin.—McINTYRE (*J. Am. Med. Assn.*, 1933, 100, 1097) reports a series of

20 cases of an unusual type of encephalitis. Hemorrhage into the spinal fluid was a prominent feature, occurring in 13 of the 20 cases. The spinal fluid pressure was definitely increased in only 3 cases. Lymphocytosis was observed in 7 cases. Increase in globulin was noted in 5 cases in which no bleeding occurred into the spinal fluid. This suggests a serous infiltration in those cases with perhaps increased permeability of the pial vessels, which in the more severe forms allowed both red and white blood cells as well as serum to escape from the blood-vessels. Somnolence, at times becoming coma, was a prominent feature as it occurred in 12 of the 20 cases. Coma was present in 9 cases. Diplopia occurred in 6 cases. Pyramidal signs were a prominent sign, occurring in 14 cases. This was in marked contrast to the epidemic of so-called lethargic encephalitis observed by the author, in which extra-pyramidal signs were more prominent than pyramidal signs. Another marked difference in the cases noted in this series from those of epidemic encephalitis was that in this series no extra-pyramidal residues were noted. Convulsions beginning with Jacksonian symptoms passing into generalized convulsions were observed in 7 cases. This indicated motor cortex irritation. Death occurred in 9 cases. Congestion of the disks occurred in 7 cases and a choked disk was observed in 2 cases. Clinically there were 3 types of cases. One group was represented by serous infiltration with clinical meningo-encephalitic signs plus increase in globulin in the spinal fluid. Another group showed clinical meningo-encephalitic symptoms with lymphocytosis in the spinal fluid. The third group was the most severe form of the disease, represented by those cases in which hemorrhage occurred in the spinal fluid, accompanied by increase in globulin and also by increased lymphocytes in the spinal fluid. It is thought that the disease is infectious in origin although no definite evidence was evoked. In differentiation a number of conditions must be considered. These include cerebral arteriosclerosis with hemorrhage; meningeal hemorrhage due to rupture of a syphilitic aneurysm; idiopathic hemorrhage as a result of status lymphaticus; brain tumor with hemorrhage from the tumor; fracture of the skull with meningeal hemorrhage, although this can usually be eliminated by the history. Although this report includes a number of adults, it was seen in a number of children, 1 being only 8 months of age.

Prevention of Scarlet Fever.—MELNICK (*Arch. Pediat.*, 1933, 50, 158) performed the Dick test on 551 children in an orphanage. Ninety-four of these children (17 per cent) were Dick positive, and 91 of these were immunized with Dick scarlet fever toxin, receiving 5 injections at weekly intervals. The following precautionary measures were found to be valuable in reducing the severity and duration of the reactions. Mild laxative, preferably milk of magnesia, was given on the night before the injections. The diet was restricted on the day before the injections to fruit juices, cereal water, tea and toast. The activities were restricted on the day before as well as the day after the injection. The injection should be given the latter part of the day, late afternoon or early evening, and preferably on Friday or on a day preceding a school holiday, so that if a reaction should appear, confining the child to bed, there will be no necessity for absence from school. The reac-

tions observed in this study were at no time alarming, nor were they productive of any complications or sequelæ such as are frequently observed even in the mild types of scarlet fever. The reactions that were encountered included headaches, nausea, vomiting, abdominal pain and fever in various combinations or separately. Ninety children were Dick tested 2 weeks after the 5th injection, and of this number 79 children (88 per cent) were Dick negative and 11 (12 per cent) were Dick positive. The 11 Dick positives who had already received 5 injections of scarlet fever toxin were given a 6th injection and were tested after 2 weeks with the result that an additional 9 children were rendered Dick negative. A total of 98 per cent of negatives were thus obtained.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Rudimentary Accessory Vagina.—An interesting development defect which has come to the attention of HALBAN (*Zentrbl. f. Gyn.*, 1932, 56, 2401) on several occasions is the existence of a band in the vagina which resembles scar tissue but which he has seen in nulliparous women who have never had operative procedures performed on them. He terms this band *plica falciformis cervico-laquearis* and states that as a rule it begins around the upper region of the portio vaginalis of the cervix and extends in an angular fashion along the lateral vaginal fornix and then toward the vulva. Its edge is usually sharp and undermined and presents a characteristic erebent shape. He believes this band represents the remains of a vaginal septum which has been displaced laterally in the course of development of the vagina. In the space between this band and the true lateral wall of the vagina is a rudimentary second vagina. If there is no communication between these two vaginas the patient may develop a lateral hematocolpos or pyocolpos. If there is a communication between the two vaginas it is possible to demonstrate the second cervix above the rudimentary vagina through the communicating opening. Such a second vaginal sac and cervix will be large or small depending on how high the atresia of the rudimentary vagina extends. When this second vagina communicates with the main vagina there will be no secretion present in the accessory vagina and the walls collapse leaving the above mentioned plica which is gradually displaced laterally. The practical importance of this observation is only that it makes the observer think of a double uterus or other defects of development in such a patient since these defects are frequently unrecognized. This contribution of the author, which has not been previously reported, adds another point of interest to the fascinating subject of defects in fusion of the Muellerian ducts.

Relief of Pain in Pelvic Carcinoma.—In the late stages of carcinoma of the female pelvic organs the pain is sometimes so intense and constant that even morphin is without avail unless given in enormous doses. In such cases GRANT (*Am. J. Obst. and Gynec.*, 1932, 24, 620) reminds us that the pain can be permanently relieved by the operation of cordotomy which sections the fibers in the anterolateral columns of the spinal cord. Following the operation there is no pain or temperature sensation below the point of section but the sensation of touch and position are unimpaired. While bilateral cordotomy takes longer to perform than the unilateral operation it is to be preferred in the treatment of pelvic cancer because it is more certain in its results. His experience is based on 25 cases of this type in 15 of which a bilateral operation was done and in 10 a unilateral. The average duration of life following the operation was 7 months. The disadvantage of the operation is that unless the incision into the cord is accurately placed, the pain may not be completely relieved or the motor pathways may be damaged, resulting in paralysis of the legs and interference with sphincter control. While this may seem to be a rather heroic type of operation to undertake in inoperable patients, the complete relief of pain during the last months of a lingering illness will at times justify its performance.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Pathologic Changes in the Orbit in Progressive Exophthalmos.—NAFFZIGER (*Arch. Ophthalm.*, 1933, 9, 1) reviews the theories on the causes of exophthalmos, ocular muscle paralysis, and optic nerve involvement in cases of exophthalmic goiter, and mentions the various treatments previously used for the relief of progressive exophthalmos. His own observations were made on 6 cases of progressive or malignant exophthalmos coming on after thyroidectomy for exophthalmic goiter. The exophthalmos varied from 26 to 35 mm. In 5 cases, ocular movements were greatly impaired, especially upward rotation. Swelling of the optic disks was present in 5 cases and impairment of vision in 5, in 1 of these without ophthalmoscopic changes. After other methods failed to control the progression of the exophthalmos, the orbits were decompressed by means of an intracranial removal of the orbital plate and the roof of the optic foramen, and opening of the orbital fascia and the ring of Zinn. The operation was successful in each instance. The globes receded gradually, the recession varying from 2 to 7 mm. without tendency to recurrence. The edema of the disks subsided rapidly and vision improved promptly. In every orbit, the extraocular muscles were found to be greatly enlarged. The muscles meas-

ured from 3 to 8 times their normal size, and showed histologically varying degrees of interstitial edema, degeneration, fibrosis and cellular infiltration. In the later phases, scar tissue and hyaline change were found in the museles. In some sections the walls of the arterioles were thickened and infiltrated by mononuclear cells. The author believes that this swelling and degeneration of the museles accounts for the exophthalmos and for the impaired ocular rotations. He adds that enlargement of the extraocular museles in cases of exophthalmos had been observed by previous investigators, but that its significance had not been properly appreciated.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Time Factors Concerned in the Germicidal Action of Ultraviolet Light.—Ultraviolet light has become a fixture in the therapeutic armamentarium of the otolaryngologist. Like many other physiotherapeutic procedures, ultraviolet light's action has been rather poorly understood and, in consequence, its clinical application has been injudiciously exploited. Therefore it behooves us to recognize basic contributions which shed a ray of light on the problem at hand. The effect of radiant energy has long been known to be the result of a certain intensity working in a given period of time, during which period a definite amount of energy is being transferred to the object irradiated. Bunsen and Roscoe have correlated these factors, and state that identical effects are obtained if the product of the intensity and time is kept constant. This, however, is merely a modification of the Schwartzschild law, which states that intensity multiplied by the time to the exponent K must equal a constant. The factor K is a number slightly less than 1, whereas the Bunsen-Roscoe law is a special case where the exponent is equal to 1, and holds true for a certain limited range of the factors (intensity and time), whereas the Schwartzschild law must be applied for excessive variations in these factors. Therefore, with marked decrease in the intensity the time must be increased more than the proportional decrease in intensity. Accordingly, BACHEM and DUSHKIN (*Proc. Soc. Exp. Biol. and Med.*, 1933, 30, 700) have experimented to ascertain whether the Schwartzschild or Bunsen-Roscoe law was applicable to the destructive effect of ultraviolet light on bacteria. The method consisted of spreading in a unicellular layer *B. prodigiosus* on an agar plate. By means of a metal shield, the area of exposure to a water-cooled Kromayer lamp can be restricted to a certain field on the plate and at the same time protect the remaining portion. The results of their carefully controlled investigations forced the authors to conclude that the intensity and duration of the exposures were not the only conditions involved, but that some other factor which must be inherent in the bacterial culture itself is also to be considered. To prove this they systematically studied the sensitivity of bacteria to equal amounts of ultraviolet light (keeping time and intensity con-

stant) and found that there was a larger or smaller sensitivity, depending upon the duration between the time of plating and time of exposure, the bacteria being kept at room temperature, 70° F. Their findings compelled the authors to compare short and long exposures of varying intensities, and to base the time comparisons on the validity of either the Bunsen-Roscoe or the Schwartzschild law. Finally, these workers maintain that the Bunsen-Roscoe law is applicable to bacterial destruction by ultraviolet light, but only for those periods in which there is no change in the bacterial sensitivity.

RADIOLOGY

UNDER THE CHARGE OF
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CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
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Leprosy.—At Kalihi Hospital, Hawaii, 140 leprosy patients were examined with the Roentgen rays by MURDOCK and HUTTER (*Am. J. Roent. and Rad. Ther.*, 1932, 28, 598). Ages of the patients ranged from 6 to 80 years; 64 per cent were from 16 to 40 years of age. Of the entire group, 108 had roentgenologic signs of osseous disease and 32 were apparently normal. Seventy-two (50 per cent) showed changes in the bones of the hands and feet. Long bones of the arms and legs showed little evidence of disease. Among 75 roentgenograms of the skull, osseous disease was manifest in only 1 instance, and in this case the patient also had syphilis. Fifty cases were chosen and studied because of marked involvement of the soft tissues of the nose and throat, but in no case was there roentgenologic evidence that the nasal bones were affected. In a few cases hyperplasia of one or more ribs was seen. The vertebrae were negative save for a few deformities and arthritides. It was found that the degree of cutaneous leprosy is not a reliable index of bone involvement, and in many cases with large leprosy nodules in the skin the bones were not affected. Leprosy lesions of bone found in this study were multiform. In many cases the changes were rather minute; in others there was extensive osteitis, osteomyelitis, or cystic degeneration, all in various degrees of dissolution, destruction and regeneration; in a third group destructive or productive arthritis was marked.

Umbrathor in Urography.—RITTER and RATTNER (*Am. J. Roent. and Radium Ther.*, 1932, 28, 629) have employed umbrathor for roentgenographic examination of the urinary bladder in 3 cases. Umbrathor is a 25 per cent solution of thorium dioxide, a stable brownish liquid, transparent in transmitted light and of milky appearance in reflected light. It is not toxic and is not absorbed by the bladder. When it comes in contact with mucosal surfaces it forms a flocculent coating

thereon and may thus be used to produce relief pictures by inflating the bladder with air after drawing off the excess fluid. In 2 cases a tumor of the bladder was demonstrated and in 1 case the bladder was normal. In a fourth case the authors used the medium to produce a vesiculogram in a case of sterility. The seminal vesicles were well outlined, but the drug remained for several weeks, the umbrathor acting apparently as an obstructing foreign body. It was felt, therefore, that this agent should not be used for vesiculography.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Auditory Hallucinations in Non-psychotic Children.—LEVIN (*Am. J. Psychiat.*, 1932, 11, 1119) presents 4 cases of boys who were nonpsychotic and had true auditory hallucinations. Two of them showed what probably are early symptoms of a schizophrenic reaction. The other 2, while maladjusted, showed nothing suggestive of schizophrenia or any other psychosis. All 4 boys were below the average in intelligence, 2 of them conspicuously so. The hallucinatory episodes were studied with regard to the quality of the hallucinatory perception, the localization, the presence of accessory sensations, the content and the apparent functions involved. The hallucinations seem to have participated in the fulfillment of the functions of: (a) defense; (b) enhancement of self-esteem; (c) satisfaction of instinctive cravings and of a desire for pleasure; (d) repression of unwelcome instinctive cravings; (e) self-punishment in expiation of a sense of guilt. It is emphasized that while certain functions are fulfilled, these probably constitute only one link in the chain of factors which really causes the hallucinations to occur. In 1 case there was evidence of mixed deafness in one ear and in another there was the possibility of some organic auditory disturbance. The significance of the findings for the general problem of projection and their relationship to recent work in eidetics are discussed.

A Combination Therapy of Induced Narcosis and Fever: Its Effect on the "Affective Syndrome."—HACKFIELD (*Arch. Neurol. and Psychiat.*, 1932, 28, 1169) states that patients suffering from the affective types of psychoses are the most desirable for this form of therapy embodying the artificial induction of fever and a prolonged narcosis. Considering the therapeutic action from the standpoint of the pathogenesis of the affective syndrome: as a result of the many afferent stimuli, conditioned reflexes are established. In the cerebrum, integration of these reflexes takes place according to definite laws. In certain human con-

stitutional types these delicate mechanisms are easily disturbed and a cycle of heterogeneous disorganized reactions follows. Their reflex actions express themselves objectively through the medium of various autonomic functions: salivary secretion or inhibition, emotional states, gastric secretion, etc. Hence, there arises the accompanying autonomic dysfunctions in these psychoses. To affect a recovery, this cycle must be broken, and rest, that is, a reduction in the afferent stimuli, is the best agent. The use of a drug, the therapeutic attack of which breaks this cycle at any point, in either the brain stem or the cerebrum, producing absolute rest, is the goal of this therapy. One is dealing with a physiopathologic process, the psychologic signs and symptoms forming merely a part of the symptom complex, though probably of a psychogenic origin. It is not claimed that after recovery the patient is guarded against further recurrences, but the induced remissions do compare favorably in duration with those obtained with other forms of treatment. However, the apparent specificity of this therapy in the affective syndrome suggests its application in suitable cases, because affective types of psychoses may thus sometimes be terminated within 3 weeks or less which otherwise might be protracted to months or years, or even become chronic.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Hepatic Lesions Associated With Eclampsia and Those Caused by Raising the Intraabdominal Pressure.—THEOBALD (*J. Pathol. and Bacteriol.*, 1932, 35, 843) studied the livers of 44 postmortem examinations of women who died from eclampsia. He found the constant feature was not hemorrhage (found in 31, not found in 13), but was degeneration of liver cells almost invariably associated with areas of necrosis. It was into these areas that hemorrhage occurred, when found. Hemorrhages were also observed in some cases in lungs, brain and kidneys. The author conducted a series of experiments on dogs and cats in which he raised the intraabdominal pressure by injection of normal saline and then using binders studied the lesions produced. These lesions were mainly of the nature of necrosis of liver cells, more apparent in the central areas but sometimes also present in the periphery. The striking feature of these results was the rapidity with which degeneration occurred. The animal which showed the most extensive necrosis was one in which repeated fits were produced of very short duration ($\frac{1}{2}$ minute). It is suggested that while hepatic dysfunction renders the human liable to eclampsia, the onset may be determined by the mechanical factors associated with the actual contractions of

labor. It is further suggested that the liver may be damaged by frequent prolonged and violent pains, associated with obstructed labor, and even that a certain amount of damage occurs during a normal labor. He offers the explanation that such damage to liver cells may be an important factor in lowering the resistance of the body to puerperal infection.

A Case Illustrating the Effects of Prolonged Action of Radium.—Ross (*J. Pathol. and Bacteriol.*, 1932, 35, 899) describes a case of advanced cancer of breast, in which a radium needle (26 originally used in treatment) of strength 2 mg. and covered by a thickness of 0.5 mm. of platinum was accidentally lost in the 4th intercostal space, and which, on Roentgen ray examination, was shown to be in the pericardium. The patient lived for 3 years after this, gradually developing cardiac insufficiency with irregularities and a late jaundice. Post-mortem failed to reveal any trace of mammary cancer, but showed a malignant hemangio-endothelioma of the liver with metastases in lungs and bone marrow. The pericardial sac was obliterated by firm adhesions. Near the radioactive focus was found complete necrosis of all tissues, the heart muscle being converted to a structureless hyaline mass. With increasing distance from the needle the necrosis was most severe in the par-arterial areas, while in the perivascular regions the survival of muscle fibers was noted. In further areas were seen hemorrhages and endothelial swelling, beyond which heart muscle was normal; the total zone of necrosis had a radius of $1\frac{1}{2}$ inches. The author ascribes the changes in heart muscle to alterations in its bloodvessels. The spleen and lymphadenoid tissues showed proliferation of macrophages, loss of follicular structure of lymphoid tissue and disappearance of lymphocytes with replacement by plasma cells, and these changes are suggested to have resulted from vascular disturbances due to irradiation. The blood picture showed a relative and absolute lymphopenia. The malignant hemangio-endothelioma in the liver, adjacent to the position of the needle, was thought to be caused by the action of prolonged irradiation on the vessels near the surface of the liver. The author concludes that this case affords additional evidence that the necrotizing and carcinogenic action of gamma radiation results from the susceptibility of the blood vascular system to irradiation.

Normal Fat Content of the Kupffer Cells.—LEVINE (*Arch. Path.*, 1932, 14, 345) presents a study of Kupffer cells in 43 presumably normal adults who met sudden death by violence. Four methods of fat staining were employed, namely Sudan III, Nile blue sulphate, Lorrain Smith-Dietrich and Ciacio. Fat was demonstrated in the Kupffer cells in no less than 41 of the 43 cases; in a few instances there was only a trace, but as a rule there were appreciable quantities. The deposit was always of the character of neutral fat which contained no doubly refracting particles. The lipid content of the Kupffer cells is roughly parallel to the lipid content of the liver cells, though the latter commonly contain doubly refracting fat whereas the former do not. No correlation seems to exist between the amount of sudanophil material in the Kupffer cells and the presence of lipid granules demonstrable by the Lorrain Smith-Dietrich method. The author concludes that neutral fat is normally found in the Kupffer cells.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Significance of Immunity Tests in Epidemiology as Illustrated in Yellow Fever.—Immunity tests are taking an important place in epidemiologic studies of several diseases of man. In diphtheria, scarlet fever and tuberculosis skin tests are commonly used. In poliomyelitis and yellow fever the serum is tested in animals, in the former by a neutralization test and in the latter by a protection test. If a result indicating immunity is obtained by any of these procedures, it is assumed that the person tested has previously been infected with the corresponding causative agent. Such evidence of a preceding immunizing infection is so frequent in persons who give no history of an attack of the disease under investigation that a high prevalence of unrecognized and subclinical cases is commonly assumed. Another possible explanation would be that the immunity tests are not so specific or so reliable as has been believed. HUGHES and SAWYER (*J. Am. Med. Assn.*, 1932, 99, 978) investigated the specificity and reliability of the yellow fever protection test in mice as an example of the immunity tests used in epidemiologic studies. Serums of persons in Canada and China who could never have been exposed to yellow fever virus were tested for protective power against this virus. In only 1 instance was there any demonstrable non-specific protective power and it was insufficient in amount to give protection with regularity. The test was found to be highly specific and useful as an indicator of past infection.

The Disinfectant Action of Certain Organic Acids.—REID (*Am. J. Hyg.*, 1932, 16, 540) states that the bactericidal activity of the monobasic series of organic acids, acetic, propionic, butyric and valeric, increases as the series is ascended, that is, with increase in molecular weight and decrease in surface tension. On the other hand, when the inhibitory values of these acids in peptone broth are considered, their activity decreases as the molecular weight decreases. This reversible toxic action of the monobasic series for bacteria, demonstrated when bactericidal and inhibitory action are compared, suggests that surface tension may play a rôle in the disinfection properties of some acids. Replacing an atom of hydrogen, in a normal monobasic acid, with a hydroxyl group, enhances the bactericidal action enormously. The hydroxy-acids of acetic and propionic are approximately 2 to 12 times as bactericidal as the normal acids against *B. pyocyaneus*, *B. typhosus* and *B. coli*. Even against such a resistant organism as *S. aureus*, they show an increased bactericidal effect. Normal mono-

basic acids, however, exert a greater inhibitory effect on bacteria than their corresponding hydroxy acids. Bactericidal power of the dibasic organic acids, oxalic, malonic and succinic, decreases as the series is ascended. The toxic action of this group against bacteria appears to parallel the degree of dissociation, the more dissociated acids having a greater bactericidal effect. Of the two tribasic acids tested, aconitic was the most toxic for bacteria. This acid was 3 to 36 times more active than citric against *B. pyocyaneus*, *B. typhosus*, *B. coli* and *S. aureus*. A wide difference exists between the ability of an acid to exert a bactericidal effect and to inhibit growth. Acids which are strongly bactericidal frequently exhibit weak inhibitory powers in liquid media. Oxalic, the most toxic acid in bactericidal dilutions, exhibited a comparatively weak inhibitory effect. Acetic, propionic and butyric acids, which are weakly bactericidal, were the most inhibitory of all the acids tested. *Bacillus pyocyaneus* is extremely sensitive to disinfection by the organic acids. Not one of these acids exerts a specific effect upon this organism. The hydrogen-ion concentration necessary to inhibit the growth of *B. pyocyaneus* in peptone broth is not constant, but varies with the kind of acid used. The monobasic acids, the least dissociated of the acids used, inhibit growth at a lower hydrogen-ion concentration than the strongly dissociated acids such as oxalic. It appears that the bactericidal action of the weaker organic acids is not alone dependent upon the anions, but that the undissociated molecules are also active in this respect.

Do Children Who Drink Raw Milk Thrive Better than Children Who Drink Heated Milk?

—There is no more vexing question confronting American parents and American health authorities than the following: Shall milk be heated before it is consumed? Most health authorities believe and teach that any milk supply, regardless of how carefully it has been produced, would be made still safer by heating it hot enough and long enough to devitalize any pathogens which might have accidentally found their way into it despite the care taken in producing it. Partly as a result of this teaching there has been a rapid increase in the percentage of milk pasteurized in the United States during the past 30 years. From the beginning of the 20th century to the present time the percentage of milk pasteurized in American cities of 10,000 population and over has increased from a negligible figure to the impressive one of 87.5 per cent. During the past several years, however, raw milk advocates have vigorously contended that heating milk adversely affects its healthfulness and growth-promoting capacity. In support of this claim repeated reference has been made to experiments conducted at Ohio State University and at the British National Institute for Research in Dairying, from which the conclusion is drawn that white rats which are fed upon heated milk will not grow as well as white rats fed upon raw milk. Raw milk advocates have used this material in publicity campaigns in many parts of the United States. They have insisted that these experiments upon white rats justify the conclusion that children will not thrive as well upon heated as upon raw milk. FRANK *et al.* (*U. S. Pub. Health Rep.*, 1932, 47, 1951) give results of studies of over 3700 children summarized for children of 10 months to 6 years of age: (1) There is no significant difference

between the average weight of children who have received no milk except heated milk and the average weight of children who have received raw milk for more than the latter half of their lives, the respective weights being 33.6 and 33.2 pounds, the insignificant difference being in favor of the children receiving heated milk. (2) The parents of the children receiving predominantly raw milk reported a higher incidence of diphtheria, scarlet fever, intestinal disturbances and rickets than did the parents of the children receiving heated milk only. These workers conclude that the growth-promoting capacity of heated milk plus the supplementary diet received by the average American child of 10 months to 6 years is not measurably less than the growth-promoting capacity of raw milk plus the supplementary diet received by the average American child of 10 months to 6 years.

The Incidence and Time Distribution of Common Colds in Several Groups Kept Under Continuous Observation.—FROST and GOVER (*U. S. Pub. Health Rep.*, 1932, 47, 1815) present data on the incidence and certain epidemiologic features of the minor respiratory diseases, as indicated by regular semimonthly reports rendered by rather large groups of students at several American universities in widely separated localities and by similar reports from some 1500 families. The students' reports cover 18 months, and the family reports extend through 2½ years. For the year ended May 30, 1925, the mean attack rate in the 10 groups of student reporters was 2947 per 1000, an average of approximately 3 attacks per person. For the entire period, and for each of its major seasonal subdivisions, the attack rates in the several student groups were remarkably uniform, showing no consistent relation to latitude, longitude or climate. In the family group, the attack rates in corresponding periods were consistently lower than in the student groups, but it is possible that this may have been due wholly or in part to more complete reporting by the students. Both in the student and the family groups, the attack rates in corresponding seasons of successive years (1923-1926) showed a declining trend. This may have been due, however, to progressive slackening of interest in reporting. Taking the mean weekly attack rate throughout the year as an axis, the weekly attack rates in each group and in each year were quite consistently below this level from about April 1 to September 1, and generally above this level from September to March, inclusive. The minimum attack rates were observed usually in the latter half of July or the first half of August. During the season of high prevalence, from September to March, inclusive, the incidence curve in each locality exhibited a series of oscillations, constituting a succession of epidemics, each of several weeks' duration, rather irregular in sequence and magnitude, but clearly not attributable to mere chance fluctuation. These epidemics in 6 student groups in widely separated localities showed a striking time correspondence of about the same order as was observed in the influenza epidemics of 1918, 1919 and 1920. Cases reported as influenza constituted about 5.6 per cent of the total reported from the student groups, from December, 1923, to May, 1925, and about 11.7 of those recorded in the family group for the same period of 18 months. While the gross attack rates from all the minor respiratory disorders tended generally to decrease throughout the period of observation, the

reported incidence of so-called influenza tended to increase, being highest in the winter of 1925-1926. The seasonal distribution of cases reported as influenza differed from that of cases classed (clinically) as coryza, in that the latter reached their highest prevalence in the autumn, while the highest incidence of influenza occurred each year in the winter or spring months. Hence, the autumn epidemics observed each year differed from those observed in the late winter and spring in that the latter comprised larger proportions of cases classed as influenza. The increased prevalence of so-called influenza observed in most of the student groups in the winter and spring of 1924-1925 coincided generally with an increase in mortality from influenza pneumonia in the cities represented. However, in individual cities the extent of the increase in mortality bore no obvious relation to that of the increase in prevalence of influenza.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 17, 1933

Influence of Posture Upon the Intraabdominal Pressure Created by Muscular Effort.—WILLIAM F. MENGERT, and DOUGLAS P. MURPHY (Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania). Measurements of maximum intraabdominal pressure which can be created by voluntary muscular effort can be made indirectly by recording pressure transmitted to an air-inflated balloon within the vagina. The apparatus, consisting of a rubber balloon and rubber cup, was fixed in the vagina by straps attached to a belt around the waist and readings were made on a mercury manometer.

Initial inflation of the vaginal balloon is of no consequence in recording pressures which can be created, provided the latter are a little more than twice the former. This was proved by testing varying initial inflation pressures both on the human subject and on an apparatus designed to simulate actual conditions as far as possible.

Various factors, of which posture was the most important, influenced the final reading. Eleven hundred and sixty-seven measurements, each representing a maximum straining effort, were made upon 5 healthy, non-pregnant women in seven different postures. The average height to which the mercury column could be raised was 13.7 cm. This represented an actual pressure of 2.65 pounds per square inch.

Among the seven postures, five (lateral prone, recumbent, semi-recumbent, squatting, and standing) were found to vary among themselves in efficiency only insofar as they were influenced by weight of the viscera. Two postures, knee-elbow and sitting, however, were found to have another factor, mechanical advantage of muscular action, in addition to the visceral weight factor.

In sitting, the most efficient posture, the average pressure created was 0.7 pound per square inch better than in lateral prone, the least efficient. Of this difference, only 0.4 pound per square inch could be explained on a visceral weight basis, leaving 0.3 pound per square inch as the greater mechanical effectiveness of the abdominal muscles in this posture.

The Effect of Adrenalin and Sympathetic Stimulation on the Resting Heat Production of the Frog's Sartorius.—EMIL BOZLER (Eldridge R. Johnson Foundation, University of Pennsylvania). The anaërobic heat production of frog's sartorius was measured using Hill's thermo-electric method. Soaking the muscle in adrenalin 1 to 2,000,000 produces a 30 to 100 per cent increase in anaërobic resting heat production. There is no increase in the tension of the muscle which might account for the increment in heat production. Parallel to this effect there is always an increase in the initial heat and tension produced in a twitch.

Stimulation of the sympathetic trunk also produces an increase in the resting heat production, which may amount to more than 200 per cent of the resting heat production before the stimulation. The effect outlasts the stimulation for about 20 seconds. It is probably of the same nature as that of adrenalin although in these experiments, contrary to Orbeli's, there was no increase in the tension produced.

The Effect of Vagotomy on Muscle Glycogen Resynthesis.—C. N. H. LONG and EDITH G. FRY (George S. Cox Medical Research Institute, University of Pennsylvania). DEBOIS (*Archiv. Intern. de Pharm. et de Thérap.*, 1931, 41, 129) has recently claimed that section of the left vagus nerve in the cat prevents the resynthesis of muscle glycogen following its depletion by exercise. Since he has previously claimed that section of this nerve abolishes the formation of muscle glycogen after glucose injection (*Archiv. Intern. de Pharm. et de Thérap.*, 1931, 41, 65), he concludes: (1) That the secretion of insulin is under the control of the left vagus nerve, and (2) that the resynthesis of muscle glycogen after exercise is also dependent upon the presence of insulin.

These conclusions carry with them implications of great importance. The first of these is that a disturbance of carbohydrate metabolism akin to that found in diabetes mellitus may be produced by an extra-pancreatic lesion; second, glycogen formation in muscle under all conditions is an insulin function and the postulates of Meyerhof, that the synthesis observed after exercise occurs from the products of muscular activity alone, are rendered unnecessary.

These questions have been reinvestigated, using the standard white rat fasted for 24 hours as a test animal in preference to the cat. After a 24-hour fast the gastrocnemius muscles of the white rat have a glycogen content that is extremely uniform from animal to animal. In our experience it is invariably 530 ± 50 mgm. per cent.

Both gastrocnemii were uniformly exercised by tetanic stimulation, one removed at once and the other after various intervals of recovery.

The vagotomized rats were studied (a) immediately after the vagotomy or (b) some 8 to 14 weeks after the operation. The vagotomies were performed either on the right or left side or on both nerves in the

abdomen. In some of the acute experiments both vagi were cut in the neck.

It should be noted at this point that the animals allowed to recover from the various vagotomies grew normally and at death had a normal blood sugar. This is in agreement with the observations of others who used dogs and rabbits.

The rate of resynthesis of muscle glycogen after exercise was entirely unaffected by the various vagotomies, whether they were acute or chronic. The actual figures were: normal rats immediately after exercise, 192 mgm. per cent; 1 hour later, 383 mgm. per cent, an increase of 191 mgm. per cent. Vagotomized rats (average of all experiments) immediately after exercise, 178 mgm. per cent; 1 hour later, 378 mgm. per cent, an increase of 200 mgm. per cent.

This difference in results is not to be explained by the species difference since equally negative findings were obtained on cats. Furthermore, work at present in progress indicates that even pancreatectomy does not abolish muscle glycogen resynthesis after exercise, a finding which is also in sharp distinction from those reported by Debois.

The Blood-shift Due to Muscular Exercise (Staircase-running).
—F. S. COTTON (Department of Physiology, University of Sydney, N.S.W., Australia). An attempt to develop a new method for determining the position of the Center of Gravity in man proved successful in that it was shown to possess the advantages of improved accuracy of result and simplicity in execution. The essence of the method is to place the subject (with appropriate precautions for measuring total length) upon a reinforced plank, balanced horizontally, which is spoken of as the balance table so that his Center of Gravity is within some reasonable distance of the fulcrum, and then to measure that distance indirectly by determining the force necessary to completely balance the system. This was accomplished by means of an accurate circular spring balance.

The method, when applied to a considerable number of subjects, gave results showing a distinctly decreased range of individual variation than reported heretofore.

Small changes of Center of Gravity are readily followed, and it is possible to make a reasonably accurate measurement of the to and fro migration of the Center of Gravity due to the movements of respiration, or to any progressive shift of mass in the body. This is accomplished by extending the balance index to constitute a writing lever and to obtain a continuous graphic record of the supporting force, from which the precise position of the Center of Gravity may be readily calculated at any moment. The most convenient procedure, however, is to consider relative changes, and to express them as so many gram centimeters of mass shift in the direction indicated.

These preliminary observations led to the idea of extending previous static investigations so as to make a dynamic study of Center of Gravity. The logical sequence was to systematize the application of the method to different circumstances, and to commence a series of studies in Center of Gravity changes, some of which have been completed and are already published.

The particular investigation which first occupied attention was concerned with an attempt to measure the change of Center of Gravity occurring as a result of muscular exercise, with the object of arriving at some conclusion as to the amount of blood which becomes mobilized in the active muscles, over and above that present in the resting state. The exercise chosen for the investigation was staircase-running, which has the advantage of bringing large muscle masses into action. The method of measuring the mass shift concerned is briefly as follows:

The subject reclines upon the balance table for some 20 or 30 minutes until equilibrium is attained. He then stands up for a period of some 5 minutes, and on reclining again to attain equilibrium, a value of the resulting mass shift is obtained indicating the effect of change of posture only. He then performs the standard staircase exercise, and reclines again until equilibrium is reached once more. The progressive drop of the balance index gives a graphic and quantitative record of the return of blood from the lower limbs in resumption of the resting distribution. Calibration of the record completes the procedure. Several difficulties arose to complicate the investigation, which had to be satisfactorily dealt with before reliable results could be secured. The two chief difficulties were: the advancement of the Center of Gravity due to the slight tilting of the table, and postexercise changes in the length of the subject.

After these difficulties had been overcome and corrections applied the net "mass shift" was determined. Further experiments were carried out in the endeavor to ascertain how much of this "mass shift" could be ascribed to "blood shift." The final value so obtained amounted on an average for some 56 male adults to 30.6 kg. cm. It was argued that if a maximum value can be arrived at for the distance factor of this mass-distance product, a minimal value may be allotted for the quantity of blood in question. Additional experiments were carried out and measurements made, to set a maximal value to this distance factor.

The conclusion was reached that in round figures, as a minimum estimate, *rather less than 500 gm. or rather more than 1 pound of blood is mobilized within the active muscles, in the case of the staircase run, beyond the amount present in the resting recumbent posture.*

The Use of Magnesium Sulphate, Avertin and Sodium Amytal With the Drinker Respirator in the Treatment of Experimental Strychnin Poisoning.—BEN T. BELL and JOSEPH STOKES, JR. (Department of Pediatrics and Laboratory of Surgical Research, University of Pennsylvania). These experiments represent an attempt to develop a practicable treatment for extreme convulsive states in children. Strychnin was used as a readily controllable convulsant and cats were used almost exclusively. The object was to discover a narcotic drug capable of controlling convulsions and insuring recovery from more than the ordinary lethal dose of the convulsant. The Drinker respirator was used to permit administration of the narcotic in dosage sufficient to paralyze respiration.

1. Influence of artificial ventilation upon the lethal dose of the anesthetic agent alone.

Magnesium sulphate, avertin, and sodium amytal were tested. Magnesium sulphate, by intramuscular and intraperitoneal injection, killed in the same dosage as in the case of animals not placed in the respirator; with intrathecal injection the lethal dose was very slightly increased by the respirator. Avertin, given subcutaneously, had irregular and uncertain narcotic effects; its lethal dose was increased from 550 to 650 mg. per kilogram by the respirator. Sodium amytal intraperitoneally proved most satisfactory: its effects were constant per unit dose, and its lethal dose was increased from 95 to 150 mg. per kilogram by the respirator.

2. Influence of narcotics and respirator upon the lethal dose of strychnin.

Magnesium sulphate, in dosage sufficient to paralyze respiration, uniformly failed to save animals poisoned with strychnin (1 mg. per kg.).

Avertin in dosage of 600 mg. per kilogram, with the respirator, was no more effective than in dosage of 450 mg. per kilogram without the respirator in saving animals poisoned with strychnin (4 mg. per kg.).

Sodium amytal, in dosage of 125 mg. per kilogram (which produced profound narcosis and complete respiratory paralysis) regularly saved animals given as much as 10 mg. of strychnin per kilogram. A smaller dose of sodium amytal (75 mg. per kg.) without the respirator saved animals poisoned with as much as 6 mg. of strychnin per kilogram.

It is concluded that magnesium does not kill by paralysis of the central nervous system alone, but probably by circulatory depression, so that the respirator does not make possible the safe use of large doses; that avertin is variable in its effects and the larger doses available when the respirator is used do not give added protection against strychnin; that sodium amytal is most promising among the three drugs in combating experimental strychnin poisoning, since with large doses of the narcotic and the respirator it is possible to save animals poisoned with 13 times the ordinary lethal dose of strychnin. This indicates also that the cause of death in strychnin poisoning is probably related to the convulsions, and not to the direct depressant action of strychnin upon the central nervous system.

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